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(54) Title: DIAGNOSTIC IMAGE ANALYSIS WITH METAL COMPLEXES

(I)

(57) Abstract

The present invention is directed to complexes represented by formula (I) wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, M, X, Y, Z and N are defined herein for use as contrast agents in diagnostic imaging.

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DIAGNOSTIC IMAGE ANALYSIS WITH METAL COMPLEXES

Background of the Invention

5

This invention relates to compounds effective as
contrast agents in diagnostic imaging. In one aspect,
this invention relates to magnetic resonance imaging
(MRI) of human or non-human animal subjects using metal
10 complexes of substituted nitrogen-containing fifteen-
membered macrocyclic ligands as contrast agents. In
another aspect, this invention relates to manganese(II)
complexes of substituted nitrogen-containing fifteen-
membered macrocyclic ligands as MRI contrast agents.

15   X-rays have long been used to produce images of
human and non-human animal tissue, e.g. the internal
organs of a patient, the patient being positioned
between a source of X-rays and a film sensitive to the
rays. Where organs interfere with the passage of the
20 rays, the film is less exposed and the resulting
developed film is indicative of the state of the organ.

More recently, nuclear magnetic resonance (NMR)
has been developed as an imaging technique, i.e. MRI.
MRI avoids the harmful effects sometimes attending X-ray
25 exposure. For improved imaging with X-rays, patients
have been given enhancers prior to imaging, either
orally or (parenterally). After a predetermined time
interval for distribution of the enhancer through the
patient, the image is taken. To obtain a good image it
30 is desirable that the time after the taking of enhancer
be kept to a minimum. On the other hand there is a
decrease in effectiveness with time, so desirably the
decay should be relatively slow so as to provide a
substantial time interval during which imaging can be
35 done.

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substantial time interval during which imaging can be
done.

In the NMR imaging process, protons in the water
of the body relax via two mechanisms referred to as T_1

5   and T_2. The rate at which the relaxation process occurs
may be altered for some water molecules by giving values
that contrast with the norm.

Compounds that enhance NMR images, referred to as
contrast agents, are generally paramagnetic in nature.

10 These may be organic free radicals or
transition/lanthanide metals which have from one to
seven unpaired electrons.

A necessary prerequisite of any ligand that binds
a metal to form a contrast agent is that the resulting

15 contrast agent be stable so as to prevent the loss of
the metal and its subsequent accumulation in the body.
Other considerations include an ability to reversibly
bind water, which in turn increases it contrastability
and decreases the dose level required. This ability is

20 clearly important since the interaction between any two
nuclear spins through space decreases at a rate equal to
the reciprocal of the distance raised to the sixth
power.

U.S. Pat. No. 4,647,447 discloses use of an NMR

25 image enhancer consisting of the salt of an anion of a
complexing acid and a paramagnetic metal anion. A
preferred embodiment is the gadolinium chelate of
diethylenetriaminepentaacetic acid (Gd DTPA), which is
now commercially available from Nycomed Salutar, Inc.

30 under the trade name Magnevist for use as an NMR
contrast agent. From the data reported therein these
appear to perform well. However, this compound is
rapidly excreted by the kidneys, making the timing of
the injection extremely critical. Furthermore, there is

35 virtually no uptake by any solid organ, such as the
heart, pancreas or liver.

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However, while a number of gadolinium contrast
agents are known, there remains the possibility that
small amounts of free lanthanides are being released, by
decomposition of the agent, into the body. Not being a
5 naturally existing metal in the body, little is known
about long term effects.

Other nitrogen-containing macrocyclic ligands
have been suggested for use as NMR contrast agents.
Jackels, S. C. et al, "Aqueous Proton NMR Relaxation
10 Enhancements by Manganese(II) Macrocyclic Complexes:
Structure-Relaxivity Relationships", Inorg. Chem., 31,
234-239 (1992) discloses fifteen-membered nitrogen-
containing ring complexes. However, these compounds
suffer from being insufficiently stable and/or colored,
15 and as such are inadequate for application as MRI
contrast agents.

Therefore, it would be highly desirable to
develop alternative contrast agents which avoid one or
more of the aforementioned disadvantages.
20 It has now been discovered that metal complexes
of substituted nitrogen-containing macrocyclic ligands
which have increased kinetic, thermodynamic and
oxidative stability, and which can be substituted to
control lipophilicity, i.e. biodistribution, avoid the
25 problems of the aforementioned contrast agents while
providing good contrastability.

SUMMARY OF THE INVENTION

30   It is an object of the invention to provide
magnetic resonance imaging (MRI) contrast agents having
improved kinetic stability, i.e. the rate at which the
paramagnetic metal dissociates from the metal complexes
of the invention. It is a further object of the
35 invention to provide MRI contrast agents in which the
biodistribution of the contrast agents can be

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controlled. It is yet a further object of the invention
to provide MRI contrast agents having improved oxidative
stability and improved hydrogen bonding. It is a still
further object of the invention to provide metal
5 complexes which are useful as X-ray or ultrasound
contrast agents, and which can be used in scintigraphy
and radiotherapy.

According to the invention, a method of magnetic
resonance imaging is provided which comprises
10 administering to a human or non-human animal subject a
contrast medium comprising a physiologically compatible
paramagnetic metal complex of the present invention and
a non-toxic, pharmaceutically acceptable carrier,
adjuvant or vehicle, and generating a magnetic residence
15 image of at least a part of the subject.

Further according to the invention, a method of
diagnostic imaging is provided which comprises
administering to a human or non-human animal subject a
diagnostic agent comprising a physiologically compatible
20 heavy metal complex of the present invention and a non-
toxic, pharmaceutically acceptable carrier, adjuvant or
vehicle, and generating an X-ray, ultrasound or
scintigraphic image of at least a part of the subject.

Further according to the invention, a method of
25 radiotherapy practiced on a human or non-human animal
subject is provided which comprises administering to the
subject a radioactive agent comprising a physiologically
compatible radioactive metal complex of the present
invention and a non-toxic, pharmaceutically acceptable
30 carrier, adjuvant or vehicle.

DETAILED DESCRIPTION OF THE INVENTION

The metal complexes of the invention used as MRI
35 contrast agents, as diagnostic agents in X-ray, ultra-

sound or scintigraphic image analysis, or as
radiotherapy agents are represented by the formula:

5

$$ \cdot(Z)_n $$

10

15

wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5,
R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently
are selected from the group consisting of hydrogen,
alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl,
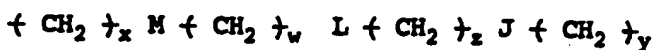20 cycloalkylalkyl, cycloalkylcycloalkyl,
cycloalkenylalkyl, alkylcycloalkyl, alkenylcycloalkyl,
alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic,
aryl and aralkyl radicals and radicals attached to the
α-carbon of α-amino acids; or R_1 or R'_1 and R_2 or R'_2, R_3
25 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7
and R_8 or R'_8, and R_9 or R'_9 and R or R' together with
the carbon atoms to which they are attached
independently form a saturated, partially saturated or
unsaturated cyclic having 3 to 20 carbon atoms; R and
30 R', R_1 and R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and
R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9
together with the carbon atoms to which they are
attached independently form a saturated, partially
saturated, or unsaturated ring structure having 3 to 20
35 carbon atoms; or one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3,
R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10},

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R_{11}, R_{12}, R_{13} and R_{14} together with a different one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} which is attached to a different carbon or nitrogen atom in

5   the macrocyclic ligand may be bound to form a strap represented by the formula

$$+ CH_2 +_x \; M + CH_2 +_w \; L + CH_2 +_z \; J + CH_2 +_y$$

wherein w, x, y and z independently are integers from 0 to 10, and M, L and J are independently selected from

10 the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, thia, sulfonyl, sulfinyl, sulfonamide, phosphonyl, phosphinyl, phosphino, phosphonium, keto, ester, carbamate, urea, thiocarbonyl, borates, boranes,

15 boraza, silyl, siloxy, silaza and combinations thereof; and R_{10}, R_{11}, R_{12}, R_{13} and R_{14} independently are selected from the group consisting of hydrogen, alkyl, and alkyl substituted with $-OR_{15}$, $-COOR_{15}$, $-CONR_{15}R_{16}$ or $-PO_3H_2$ wherein R_{15} and R_{16} are independently hydrogen or alkyl;

20 and wherein at least two of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are other than hydrogen.

X, Y and Z represent suitable ligands or charge-neutralizing anions which are derived from any

25 monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof (for example benzoic acid or benzoate anion, phenol or phenoxide anion, alcohol or alkoxide anion). X, Y and Z are independently selected from the group consisting of

30 halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen, peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide,

35 cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl

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isonitrile, nitrate, nitrite, azido, alkyl sulfonic
acid, aryl sulfonic acid, alkyl sulfoxide, aryl
sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid,
aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic
5   acid, alkyl thiol carboxylic acid, aryl thiol carb-
oxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol
thiocarboxylic acid, alkyl carboxylic acid (such as
acetic acid, trifluoroacetic acid, oxalic acid), aryl
carboxylic acid (such as benzoic acid, phthalic acid),
10   urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea,
alkyl thiourea, aryl thiourea, alkyl aryl thiourea,
sulfate, sulfite, bisulfate, bisulfite, thiosulfate,
thiosulfite, hydrosulfite, alkyl phosphine, aryl
phosphine, alkyl phosphine oxide, aryl phosphine oxide,
15   alkyl aryl phosphine oxide, alkyl phosphine sulfide,
aryl phosphine sulfide, alkyl aryl phosphine sulfide,
alkyl phosphonic acid, aryl phosphonic acid, alkyl
phosphinic acid, aryl phosphinic acid, alkyl phosphinous
acid, aryl phosphinous acid, phosphate, thiophosphate,
20   phosphite, pyrophosphite, triphosphate, hydrogen
phosphate, dihydrogen phosphate, alkyl guanidino, aryl
guanidino, alkyl aryl guanidino, alkyl carbamate, aryl
carbamate, alkyl aryl carbamate, alkyl thiocarbamate
aryl thiocarbamate, alkyl aryl thiocarbamate, alkyl
25   dithiocarbamate, aryl dithiocarbamate, alkyl aryl
dithiocarbamate, bicarbonate, carbonate, perchlorate,
chlorate, chlorite, hypochlorite, perbromate, bromate,
bromite, hypobromite, tetrahalomanganate,
tetrafluoroborate, hexafluorophosphate,
30   hexafluoroantimonate, hypophosphite, iodate, periodate,
metaborate, tetraaryl borate, tetra alkyl borate,
tartrate, salicylate, succinate, citrate, ascorbate,
saccharinate, amino acid, hydroxamic acid,
thiotosylate, and anions of ion exchange resins, or
35   systems where one or more of X,Y and Z are independently
attached to one or more of the "R" groups, wherein n is

an integer from 0 to 3. The preferred ligands from which X, Y and Z are selected include halide, organic acid, nitrate and bicarbonate anions.

The metal atoms or anions, M, which are suitable for use in the complexes of the invention as MRI contrast agents are paramagnetic metals having atomic numbers 21-29, 42-44 and 57-71. The complexes for use as MRI contrast agents are those wherein the preferred metal is Eu, Gd, Dy, Ho, Cr, Mn or Fe, more preferably Gd(III) or Mn(II), and most preferably Mn(II).

The metal atoms or anions, M, which are suitable for use in the complexes of the invention as X-ray or ultrasound contrast agents are heavy metals having atomic numbers 20-32, 42-44, 49 and 57-83. The complexes for use as X-ray or ultrasound contrast agents are those wherein the preferred metal is a non-radioactive metal having atomic numbers 42-44, 49 and 57-83, and most preferably Gd, Dy or Yb.

The metal atoms or anions, M, of the complexes of the invention which are suitable for use in scintigraphic and radiotherapy are radioactive metals of any conventional complexable radioactive metal isotope, preferably those having atomic numbers 20-32, 42-44, 49 and 57-83. In scintigraphy, the most preferred metals are ^{99m}Tc or ^{111}In. In radiotherapy, the most preferred metals are ^{153}Sm, ^{67}Cu or ^{90}Y.

As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to about 22 carbon atoms, preferably from about 1 to about 18 carbon atoms, and most preferably from about 1 to about 12 carbon atoms. Examples of such radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, octadecyl and eicosyl. The term "alkenyl",

alone or in combination, means an alkyl radical having
one or more double bonds. Examples of such alkenyl
radicals include, but are not limited to, ethenyl,
propenyl, 1-butenyl, cis-2-butenyl, trans-2-butenyl,
5   iso-butylenyl, cis-2-pentenyl, trans-2-pentenyl, 3-
methyl-1-butenyl, 2,3-dimethyl-2-butenyl, 1-pentenyl,
1-hexenyl, 1-octenyl, decenyl, dodecenyl, tetradecenyl,
hexadecenyl, cis- and trans- 9-octadecenyl, 1,3-
pentadienyl, 2,4-pentadienyl, 2,3-pentadienyl, 1,3-
10 hexadienyl, 2,4-hexadienyl, 5,8,11,14-eicosatetraenyl,
and 9,12,15-octadecatrienyl. The term "alkynyl", alone
or in combination, means an alkyl radical having one or
more triple bonds. Examples of such alkynyl groups
include, but are not limited to, ethynyl, propynyl
15 (propargyl), 1-butynyl, 1-octynyl, 9-octadecynyl, 1,3-
pentadiynyl, 2,4-pentadiynyl, 1,3-hexadiynyl, and 2,4-
hexadiynyl. The term "cycloalkyl", alone or in
combination means a cycloalkyl radical containing from 3
to about 10, preferably from 3 to about 8, and most
20 preferably from 3 to about 6, carbon atoms. Examples of
such cycloalkyl radicals include, but are not limited
to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cycloheptyl, cyclooctyl, and perhydronaphthyl. The term
"cycloalkylalkyl" means an alkyl radical as defined
25 above which is substituted by a cycloalkyl radical as
defined above. Examples of cycloalkylalkyl radicals
include, but are not limited to, cyclohexylmethyl,
cyclopentylmethyl, (4-isopropylcyclohexyl)methyl, (4-t-
butyl-cyclohexyl)methyl, 3-cyclohexylpropyl, 2-cyclo-
30 hexylmethylpentyl, 3-cyclopentylmethylhexyl, 1-(4-
neopentylcyclohexyl)methylhexyl, and 1-(4-
isopropylcyclohexyl)methylheptyl. The term
"cycloalkylcycloalkyl" means a cycloalkyl radical as
defined above which is substituted by another cycloalkyl
35 radical as defined above. Examples of
cycloalkylcycloalkyl radicals include, but are not

limited to, cyclohexylcyclopentyl and
cyclohexylcyclohexyl. The term "cycloalkenyl", alone or
in combination, means a cycloalkyl radical having one or
more double bonds. Examples of cycloalkenyl radicals
5   include, but are not limited to, cyclopentenyl,
cyclohexenyl, cyclooctenyl, cyclopentadienyl,
cyclohexadienyl and cyclooctadienyl. The term
"cycloalkenylalkyl" means an alkyl radical as defined
above which is substituted by a cycloalkenyl radical as
10 defined above. Examples of cycloalkenylalkyl radicals
include, but are not limited to, 2-cyclohexen-1-
ylmethyl, 1-cyclopenten-1-ylmethyl, 2-(1-cyclohexen-1-
yl)ethyl, 3-(1-cyclopenten-1-yl)propyl, 1-(1-cyclohexen-
1-ylmethyl)pentyl, 1-(1-cyclopenten-1-yl)hexyl, 6-(1-
15 cyclohexen-1-yl)hexyl, 1-(1-cyclopenten-1-yl)nonyl and
1-(1-cyclohexen-1-yl)nonyl. The terms "alkylcycloalkyl"
and "alkenylcycloalkyl" mean a cycloalkyl radical as
defined above which is substituted by an alkyl or
alkenyl radical as defined above. Examples of
20 alkylcycloalkyl and alkenylcycloalkyl radicals include,
but are not limited to, 2-ethylcyclobutyl, 1-
methylcyclopentyl, 1-hexylcyclopentyl, 1-
methylcyclohexyl, 1-(9-octadecenyl)cyclopentyl and 1-(9-
octadecenyl)cyclohexyl. The terms "alkylcycloalkenyl"
25 and "alkenylcycloalkenyl" means a cycloalkenyl radical
as defined above which is substituted by an alkyl or
alkenyl radical as defined above. Examples of
alkylcycloalkenyl and alkenylcycloalkenyl radicals
include, but are not limited to, 1-methyl-2-cyclopentyl,
30 1-hexyl-2-cyclopentenyl, 1-ethyl-2-cyclohexenyl, 1-
butyl-2-cyclohexenyl, 1-(9-octadecenyl)-2-cyclohexenyl
and 1-(2-pentenyl)-2-cyclohexenyl. The term "aryl",
alone or in combination, means a phenyl or naphthyl
radical which optionally carries one or more
35 substituents selected from alkyl, cycloalkyl,
cycloalkenyl, phenyl, naphthyl, heterocycle, alkoxyaryl,

alkaryl, alkoxy, halogen, hydroxy, amine, cyano, nitro, alkylthio, phenoxy, ether, trifluoromethyl and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-

5   hydroxyphenyl, 1-naphthyl, 2-naphthyl, and the like. The term "aralkyl", alone or in combination, means an alkyl or cycloalkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, 2-phenylethyl, and the

10 like. The term "heterocyclic" means ring structures containing at least one other kind of atom, in addition to carbon, in the ring. The most common of the other kinds of atoms include nitrogen, oxygen and sulfur. Examples of heterocyclics include, but are not limited

15 to, pyrrolidinyl, piperidyl, imidazolidinyl, tetrahydrofuryl, tetrahydrothienyl, furyl, thienyl, pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrazinyl, indolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridinyl, benzoxadiazolyl, benzothiadiazolyl, triazolyl

20 and tetrazolyl groups. The term "saturated, partially saturated or unsaturated cyclic" means fused ring structures in which 2 carbons of the ring are also part of the fifteen-membered macrocyclic ligand. The ring structure can contain 3 to 20 carbon atoms, preferably 5

25 to 8 carbon atoms, and can also contain one or more other kinds of atoms in addition to carbon. The most common of the other kinds of atoms include nitrogen, oxygen and sulfur. The ring structure can also contain more than one ring. The term "saturated, partially

30 saturated or unsaturated ring structure" means a ring structure in which one carbon of the ring is also part of the fifteen-membered macrocyclic ligand. The ring structure can contain 3 to 20, preferably 5 to 8, carbon atoms and can also contain nitrogen, oxygen and/or

35 sulfur atoms. The term "organic acid anion" refers to carboxylic acid anions having from about 1 to about 18

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carbon atoms. The term "halide" means chloride or
bromide.

       The overall charge-type of the complex can be
varied from negative to positive by nitrogen or carbon
5 substitution of the appropriate charged groups on the
macrocyclic framework.   While the manganese (II)
complexes of the invention exist as monocations in
methanol solution, the axial anions are labile and in
vivo can rapidly exchange with endogenous charged or
10 uncharged ligands. By considering the dispositive
nature of the manganese (II) metal center, the overall
charge on the complex can be adjusted as needed to
enhance desired pharmaceutical properties such as
osmolality, tissue distribution and non-target
15 clearance. For example, if the complex carries only
charge neutral functionality, such as N- or C-alkyl
substitution, then the overall charge on the complex
will be determined by the manganese center and will be
positive. Multi-positive complexes are available via
20 the incorporation of pendant cations such as protonated
aminoalkyl groups. These types of complexes can bind to
endogenous anions, anionic proteins, cell membranes, and
the like. If two pendant anionic groups are attached,
such as two carboxylates, phenolate, phosphonates,
25 sulfonates and the like, the overall charge on the
complex can be envisioned as zero. Alternatively, if
three or more pendant anionic groups are attached, the
an anionic complex will result. The pendant groups may
be designed to axially chelate and formally displace the
30 axial anions or they may be designed specifically to not
chelate but retain a charge type.

       The substitutents on the complex of the invention,
i.e. the "R" groups other than hydrogen, are those
groups which result in complexes having improved
35 stability, controlled lipophilicity, improved hydrogen
bonding and greater rigidity of the macrocyclic ligand.

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Regarding rigidity of the macrocycle, groups which rigidify the macrocycle result in improved stability and improved inner- and outer-sphere relaxation. Examples of groups which improve rigidity of the macrocycle

5 include, but are not limited to, cycloalkyl groups e.g. trans-cyclohexano, and multiple alkyl groups, e.g. pentamethyl.

Regarding hydrogen bonding, groups that improve hydrogen bonding result in improved residence time of

10 water to the metal complex by providing alternate binding sites. Examples of groups that improve hydrogen bonding include, but are not limited to, hydroxy alkyl, e.g. hydroxymethyl.

By varying the type and number of substitutents,

15 e.g. "R" groups which are other than hydrogen, the lipophilicity of the complexes can be controlled, i.e. the biodistribution of the complexes of the invention can be controlled, by preparing compounds which vary from hydrophilic to lipophilic. Therefore, the

20 complexes of the invention can be targeted to various tissues or organs in the body by controlling the type and number of substitutents.

Kinetic stability of the metal complex is important because complexes which are not sufficiently kinetically

25 stable dissociate and release free metal in the body. The kinetic stability, k_{diss} ($M^{-1}sec^{-1}$), can be controlled by varying the type and number of substitutents which are other than hydrogen. The complexes of the invention have $k_{diss} \leq$ to 1400 $M^{-1}sec^{-1}$, i.e. the complexes of the

30 invention are at least twice as stable as the complex in which all R's are hydrogen. In addition, the type and number of substitutents can be selected to give complexes which are at least 1000 times more kinetically stable than the complex in which all R's are hydrogen.

35 Examples of groups that improve kinetic stability include, but are not limited to, cycloalkyl groups, e.g.

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trans-cyclohexano, and multiple alkyl groups, e.g.
penta- methyl. Oxidative stability of the metal complex
is a particular problem for Mn complexes and is
important because complexes which are not sufficiently
5   oxidatively stable will go from Mn(II) to Mn(III).
Since the Mn(III) complexes are colored, it is necessary
to maintain the complexes in the Mn(II) form to have an
effective contrast agent. By varying the type and
number of substitutents, the oxidative stability,
10 $E_{1/2}(v)$, is controlled. It is generally desired to
select the type of number of substitutents such that $E_{1/2}$
is greater than about 0.7v.
     The number of "R" groups attached to carbon atoms,
i.e. $R-R_9$ and $R'-R_9'$, which are other than hydrogen is
15 preferably at least 3, and more preferably at least 5.
     One group of currently preferred compounds are
those in which at least one of R_1 or R'_1 and R_2 or R'_2,
R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or
R'_7 and R_8 or R'_8, and R_9 or R'_9 and R or R' together
20 with the carbon atoms to which they are attached form a
saturated cyclic having 5 to 8 carbon atoms; and all of
the remaining "R" groups are independently selected from
hydrogen, alkyl, or alkyl substituted with $-OR_{15}$ or
$-NR_{15}R_{16}$ wherein R_{15} and R_{16} are independently hydrogen or
25 alkyl. The number of saturated cyclic rings can vary
from one to 5, but is preferably at least 2, and the
most preferred saturated cyclic has a ring size of 6
carbon atoms, i.e. is a cyclohexano group. An example
of such a compound is represented by the formula:

30

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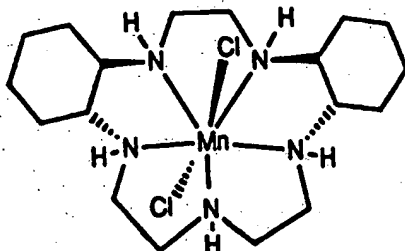
-15-

Another group of currently preferred compounds are those in which at least two of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are alkyl or alkyl substituted with $-OR_{15}$ or $-NR_{15}R_{16}$ wherein R_{15} and R_{16} are independently hydrogen or alkyl. The number of "R" groups which are alkyl or substituted alkyl is preferably at least 3, and more preferably at least 5. An example of such a compound is represented by the formula:
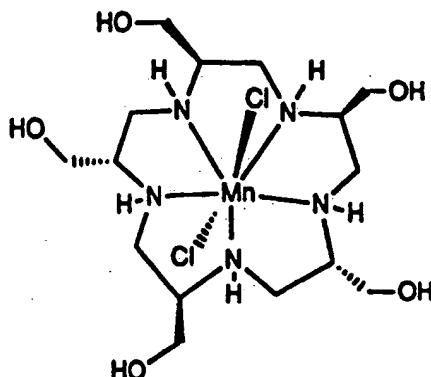
A first embodiment of the invention relates to the above metal complexes wherein at least one of R_{10}, R_{11}, R_{12}, R_{13} and R_{14} is other than hydrogen.

A second embodiment of the invention relates to a method of magnetic resonance imaging comprising (a) administering to a human or non-human animal subject a contrast medium comprising a physiologically compatible complex of the invention and a nontoxic pharmaceutically acceptable carrier, adjuvant or vehicle; and (b) generating a magnetic resonance image of at least a part of the human or non-human animal subject.

A third embodiment of the invention relates to a method of diagnostic imaging comprising (a) administering to a human or non-human animal subject a diagnostic agent comprising a physiologically compatible complex of the present invention and a nontoxic, pharmaceutically acceptable carrier, adjuvant or

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vehicle, and (b) generating an X-ray, ultrasound or
scintigraphic image of at least a part of the human or
non-human animal subject.

A fourth embodiment of the invention relates to a
5 method of radiotherapy practiced on a human or non-human
animal subject comprising administering to the human or
non-human animal subject a radioactive agent comprising
a physiologically compatible complex of the present
invention wherein M is a radioactive metal, and a
10 nontoxic, pharmaceutically acceptable carrier, adjuvant
or vehicle.

The macrocyclic ligand used herein as a comparison
to the complexes of the present invention wherein all
R's are H can be prepared according to the general
15 synthetic scheme A set forth below utilizing methods
known in the art for preparation of certain
intermediates and certain ligands. See, for example,
Richman et al., *J. Am. Chem. Soc.*, 96, 2268 (1974);
Atkins et al. *Org. Synth.*, 58, 86 (1978); and EP 287
20 465. Thus a triazaalkane is tosylated in a suitable
solvent system to produce the corresponding tris(N-
tosyl) derivative. Such derivative is then treated with
a suitable base to produce the corresponding
disulfonamide anion. The disulfonamide anion is then
25 reacted with a di-O-tosylated di-N-tosylated diazaalkane
diol to produce the corresponding
pentatosylpentaazacycloalkane. The tosyl groups are
then removed and the resulting compound is reacted with
a manganese(II) compound under essentially anhydrous and
30 anaerobic conditions to form the corresponding
manganese(II) pentaazacycloalkane complex.

The macrocyclic ligands useful in the complexes of
the present invention, wherein R_1, R'_1, R_3, R'_3, R_5,
R'_5, R_7, R'_7, R_9 and R'_9 can be H or any functionality as
35 previously described, can be prepared according to the
general peptide method shown in Scheme B set forth

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below. The procedure for preparing the cyclic peptide
precursors from the corresponding linear peptides are
the same or significant modifications of methods known
in the art. See, for example, Veber, D.F. et al., J.
5   Org. Chem., 44, 3101 (1979). The general method
outlined in Scheme B below is an example utilizing the
sequential solution-phase preparation of the
functionalized linear pentapeptide from N-terminus to
C-terminus. Alternatively, the reaction sequence to
10 prepare the linear pentapeptide can be carried out by
solid-phase preparation utilizing methods known in the
art. The reaction sequence could be conducted from
C-terminus to N-terminus and by convergent approaches
such as the coupling of di- and tri-peptides as needed.
15 Thus a Boc-protected amino acid is coupled with an amino
acid ester using standard peptide coupling reagents.
The new Boc-dipeptide ester is then saponified to the
free acid which is coupled again to another amino acid
ester. The resulting Boc-tri-peptide ester is again
20 saponified and this method is continued until the Boc-
protected pentapeptide free acid has been prepared. The
Boc protecting group is removed under standard
conditions and the resulting pentapeptide or salt
thereof is converted to the cyclic pentapeptide. The
25 cyclic pentapeptide is then reduced to the
pentaazacyclopentadecane with lithium aluminum hydride
or borane. The final ligand is then reacted with a
manganese(II) compound under essentially anaerobic
conditions to form the corresponding manganese(II)
30 pentaazacyclopentadecane complex.

    Scheme B was utilized for the synthesis of the
complexes of Examples 3 and 5.

    The R groups in the macrocycles produced by the
cyclic peptide route, i.e., R_1, R'_1, R_3, R'_3, R_5, R'_5,
35 R_7, R'_7, R_9 and R'_9, could be derived from the D or L
forms of the amino acids Alanine, Aspartic acid,

Arginine, Asparagine, Cysteine, Glycine, Glutamic acid,
Glutamine, Histidine, Isoleucine, Leucine, Lysine,
Methionine, Proline, Phenylalanine, Serine, Tryptophan,
Threonine, Tyrosine, Valine and /or the R groups of

5 unnatural α-amino acids such as alkyl, ethyl, butyl,
tert-butyl, cycloalkyl, phenyl, alkenyl, allyl, alkynyl,
aryl, heteroaryl, polycycloalkyl, polycycloaryl,
polycycloheteroaryl, imines, aminoalkyl, hydroxyalkyl,
hydroxyl, phenol, amine oxides, thioalkyl,

10 carboalkoxyalkyl, carboxylic acids and their
derivatives, keto, ether, aldehyde, amine, nitrile,
halo, thiol, sulfoxide, sulfone, sulfonic acid, sulfide,
disulfide, phosphonic acid, phosphinic acid, phosphine
oxides, sulfonamides, amides, amino acids, peptides,

15 proteins, carbohydrates, nucleic acids, fatty acids,
lipids, nitro, hydroxylamines, hydroxamic acids,
thiocarbonyls, borates, boranes, boraza, silyl, siloxy,
silaza, and combinations thereof.

        The macrocyclic ligands useful in the complexes
20 of the present invention can also be prepared by the
diacid dichloride route shown in Scheme C set forth
below. Thus, a triazaalkane is tosylated in a suitable
solvent system to produce the corresponding tris(N-
tosyl) derivative. Such a derivative is treated with a

25 suitable base to produce the corresponding disulfonamide
anion. The disulfonamide anion is dialkylated with a
suitable electrophile to produce a derivative of a
dicarboxylic acid. This derivative of a dicarboxylic
acid is treated to produce the dicarboxylic acid, which

30 is then treated with a suitable reagent to form the
diacid dichloride. The desired vicinal diamine is
obtained in any of several ways. One way which is
useful is the preparation from an aldehyde by reaction
with cyanide in the presence of ammonium chloride

35 followed by treatment with acid to produce the alpha
ammonium nitrile. The latter compound is reduced in the

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presence of acid and then treated with a suitable base
to produce the vicinal diamine. Condensation of the
diacid dichloride with the vicinal diamine in the
presence of a suitable base forms the tris(tosyl)diamide
5   macrocycle. The tosyl groups are removed and the amides
are reduced and the resulting compound is reacted with a
manganese (II) compound under essentially anhydrous and
anaerobic conditions to form the corresponding
substituted pentaazacycloalkane manganese (II) complex.
10   Scheme C was utilized for the synthesis of the
complexes of Example 2.
         The vicinal diamines have been prepared by the
route shown (known as the Strecker synthesis) and
vicinal diamines were purchased when commercially
15 available. Any method of vicinal diamine preparation
could be used.
         The macrocyclic ligands useful in the complexes of
the present invention can also be prepared by the
bis(haloacetamide) route shown in Scheme D set forth
20 below. Thus a triazaalkane is tosylated in a suitable
solvent system to produce the corresponding tris(N-
tosyl) derivative. Such a derivative is treated with a
suitable base to produce the corresponding disulfonamide
anion. A bis(haloacetamide), e.g., a
25 bis(chloroacetamide), of a vicinal diamine is prepared
by reaction of the diamine with an excess of haloacetyl
halide, e.g., chloroacetyl chloride, in the presence of
a base. The disulfonamide anion of the tris(N-tosyl)
triazaalkane is then reacted with the
30 bis(chloroacetamide) of the diamine to produce the
substituted tris(N-tosyl)diamide macrocycle. The tosyl
groups are removed and the amides are reduced and the
resulting compound is reacted with a manganese (II)
compound under essentially anhydrous and anaerobic
35 conditions to form the corresponding substituted
pentaazacycloalkane manganese (II) complex.

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Scheme D is an alternative synthetic route to the complex of Example 2.

The macrocyclic ligands useful in the complexes of the present invention, wherein R_1, R'_1, R_2, R'_2 are part
5   of a *cis*- or *trans*- cycloalkyl ring system and R_5, R'_5, R_7, R'_7 and R_9, R'_9 can be H or any functionality previously described, can be prepared according to the pseudo-peptide method shown in Scheme E set forth below. A *cis*-1,2-Diaminocycloalkane or a *trans*-(R,R)-1,2-
10   diaminocycloalkane or *trans*-(S,S)-1,2-diaminocycloalkane can be used in this method in combination with any amino acids. This allows the relative stereochemistry of the cycloalkane fused ring and substituent, R_5, R'_5, R_7, R'_7, R_9, R'_9, functionality and stereochemistry to be defined
15   in any manner. As an example *trans*-(R,R)-1,2-diaminocyclhexane was monotosylated and reacted with Boc anhydride to afford the differentiated N-Boc, N-tosyl derivative. The sulfonamide was alkylated with methyl bromoacetate using sodium hydride as the base and
20   saponified to the free acid. The cyclohexanediamine containing N-tosylglycine serves as a dipeptide surrogate in standard solution-phase peptide synthesis. Thus, coupling with a functionalized amino acid ester affords the corresponding pseudo-tripeptide. Two
25   sequential TFA cleavage-couplings affords the pseudo-pentapeptide which can be N- and C-terminus deprotected in one step using HCl/AcOH. DPPA mediated cyclization followed by LiAlH$_4$ or Borane reduction affords the corresponding macrocylic ligand. This ligand system is
30   reacted with a manganese (II) compound, such as manganese (II) chloride under essentially anaerobic conditions to form the corresponding functionalized manganese (II) pentaazacycloalkane complex.

The macrocyclic ligands useful in the complexes of
35   the present invention, wherein R_1, R'_1, R_2, R'_2 and R_5, R'_5, R_6, R'_6, are part of a *cis*- or *trans*- cycloalkyl

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ring system and R_9, R'_9 can be H or any functionality
previously described, can be prepared according to the
iterative pseudo-peptide method shown in Scheme F set
forth below. A *cis*-1,2-Diaminocycloalkane or a *trans*-
5 (R,R)-1,2-diaminocycloalkane or *trans*-(S,S)-1,2-
diaminocycloalkane can be used in any combination with
each other using this method and in combination with any
amino acids. This allows the relative stereochemistry
of both cycloalkane fused rings and substituent, R_9, R'_9,
10 functionality and stereochemistry to be defined in any
manner. Thus, the (S,S)-1,2-diaminocyclohexyl-N-
tosylglycine dipeptide surrogate, prepared from (S,S)-
1,2-diaminocyclohexane exactly as in Scheme E in the
case of (R,R)-1,2-diaminocyclohexane, can be coupled
15 with a functionalized amino acid ester to afford the
corresponding pseudo-tripeptide. TFA cleavage affords
the pseudo-tripeptide TFA salt which is coupled with
(R,R)-diaminocyclohexyl-N-tosylglycine. Saponification
and TFA cleavage affords the bis-cyclohexano containing
20 pseudo-pentapeptide. DPPA mediated cyclization followed
by LiAlH$_4$ or Borane reduction affords the corresponding
bis-cyclohexano-fused macrocylic ligand. This ligand
system is reacted with a manganese (II) compound, such
as manganese (II) chloride under essentially anaerobic
25 conditions to form the corresponding functionalized
manganese (II) pentaazacycloalkane complex.

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SCHEME A

Scheme A
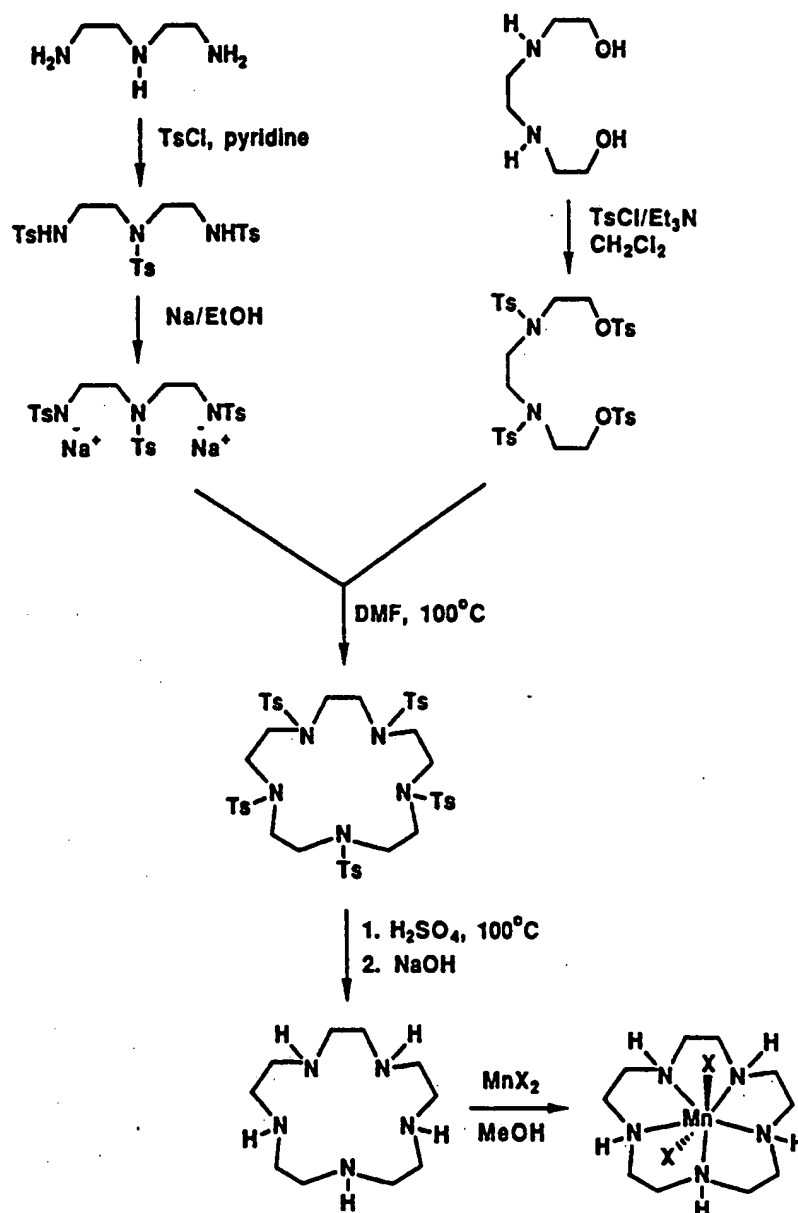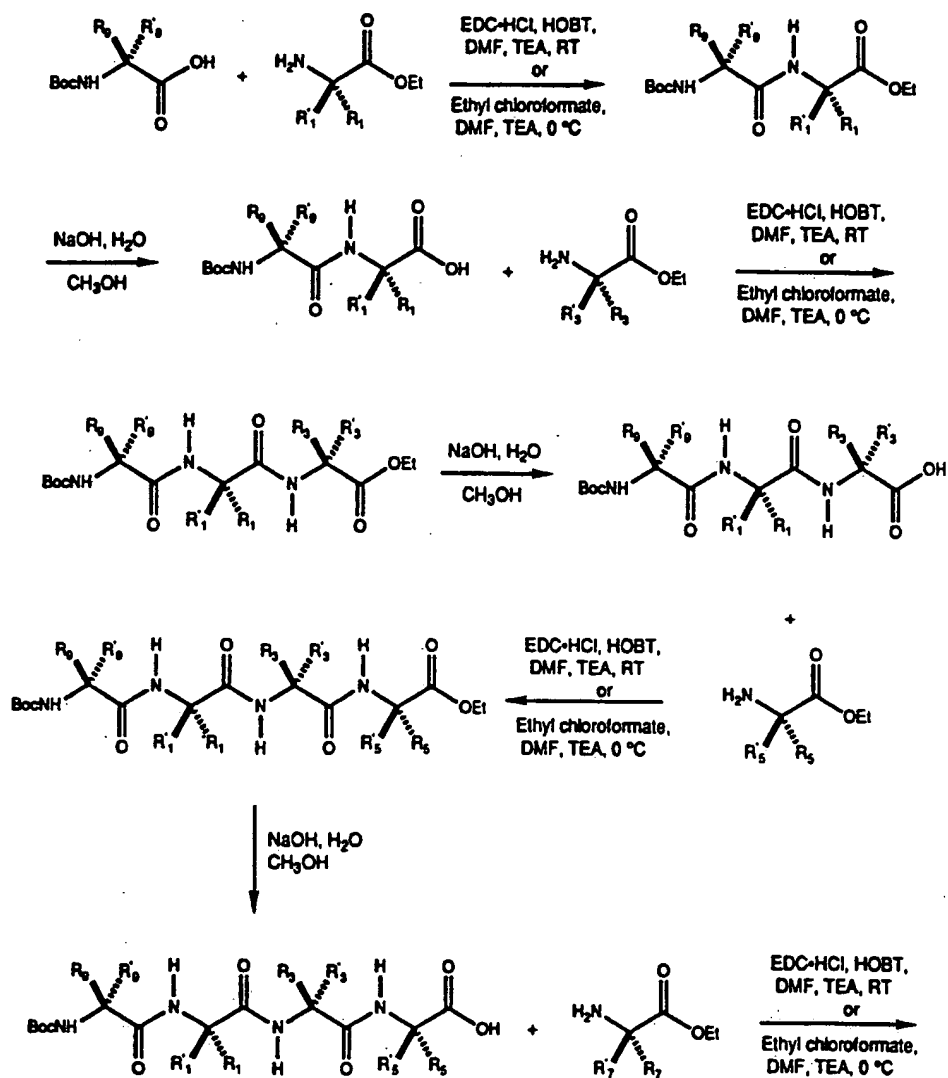
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SCHEME B

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SCHEME B (Con't.)

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SCHEME C

SCHEME D

SCHEME E

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SCHEME E (Con't.)

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SCHEME F

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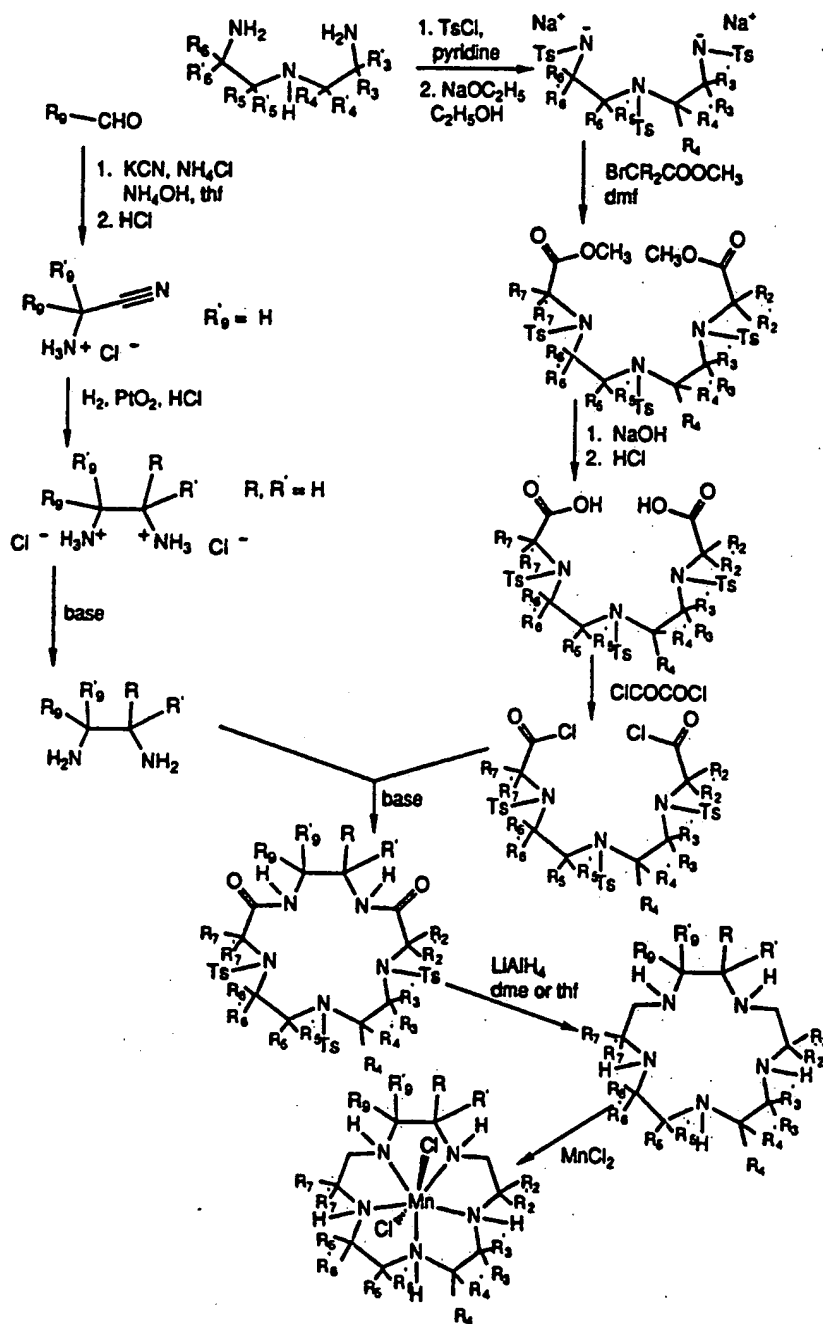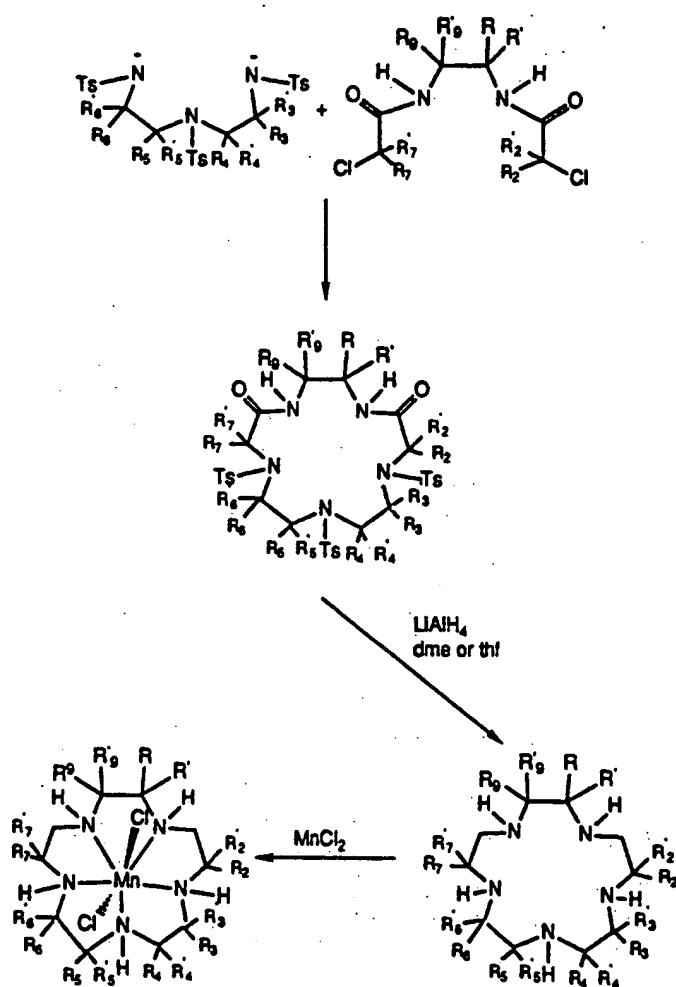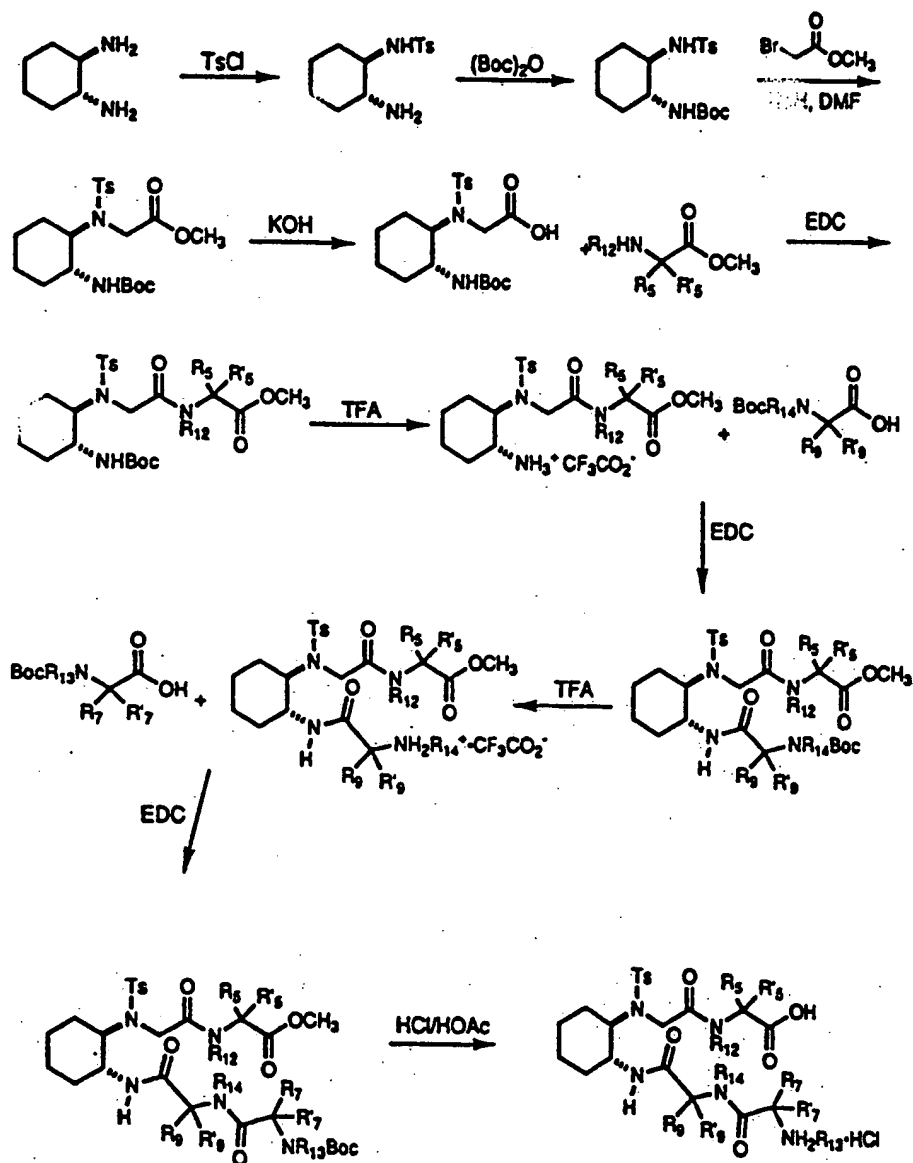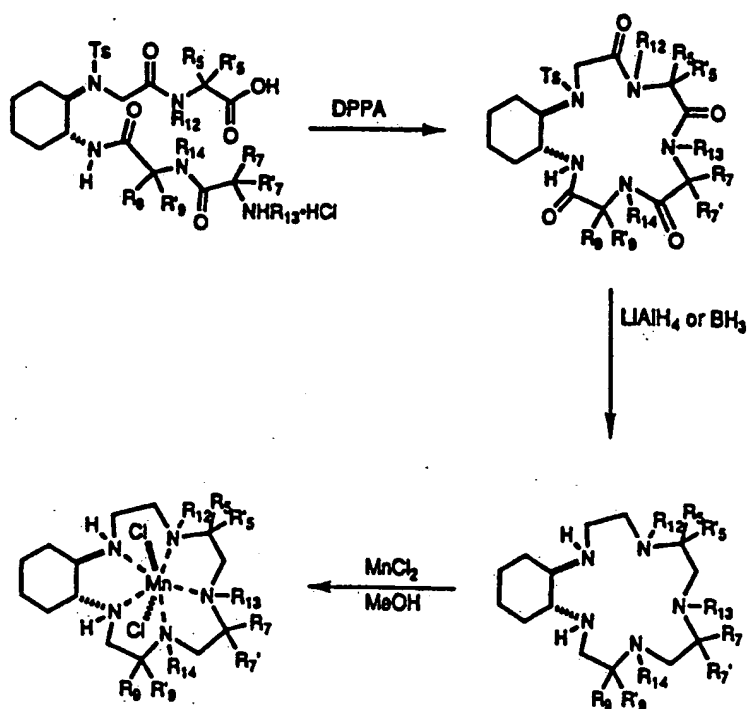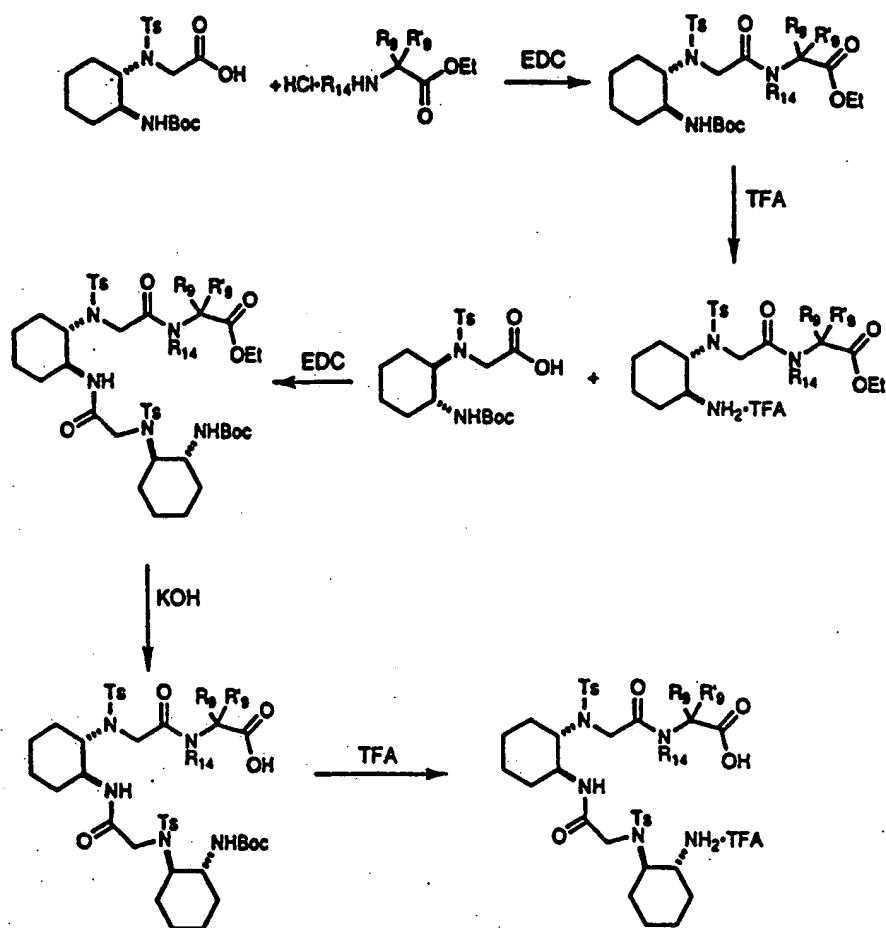
SCHEME F (Con't.)
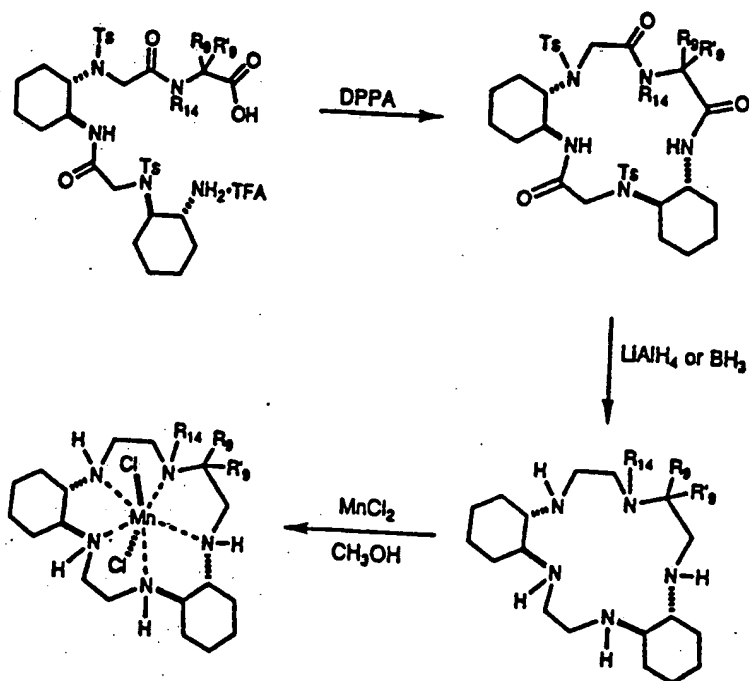
-31-

The macrocyclic ligands useful in the preparation of complexes of the present invention containing a strap can be prepared according to the following example schemes.

5   The macrocyclic ligands useful in the complexes of the present invention, wherein R_4 or R'_4 and R_8 or R'_8 are connected to one another through a "strap" or second ring system in a bicyclic sense, R_{12}, R_{13} and R_{14} can be H or any functionality previously described and R_{17} has

10   the same definition as R_{12}, R_{13} and R_{14} can be prepared according to the method set forth in Scheme G below. The TFA salt of trans-(R,R)-1,2-diaminocyclohexyl-N-tosylglycine dipeptide surrogate is coupled with Z-Glu(OtBu)-OH using EDC in DMF. This tripeptide is

15   then saponified and coupled with Orn(Boc)-OMe•HCl using EDC in DMF. The resulting tetrapeptide is then N-deprotected by hydrogenolysis of the Z group and coupled with Z-Gly again using EDC in DMF. Saponification and hydrogenolysis affords the

20   deprotected pseudopentapeptide which is cyclized with DPPA. The side chains are then deprotected in one step using TFA and a second "strap-cyclization" is effected again with DPPA as the coupling agent. Lithium aluminum hydride reduction affords the bicyclic ligand system

25   which is reacted with manganese (II) chloride under essentially anaerobic conditions to form the corresponding functionalized manganese (II) hexaazabicycloalkane complex.
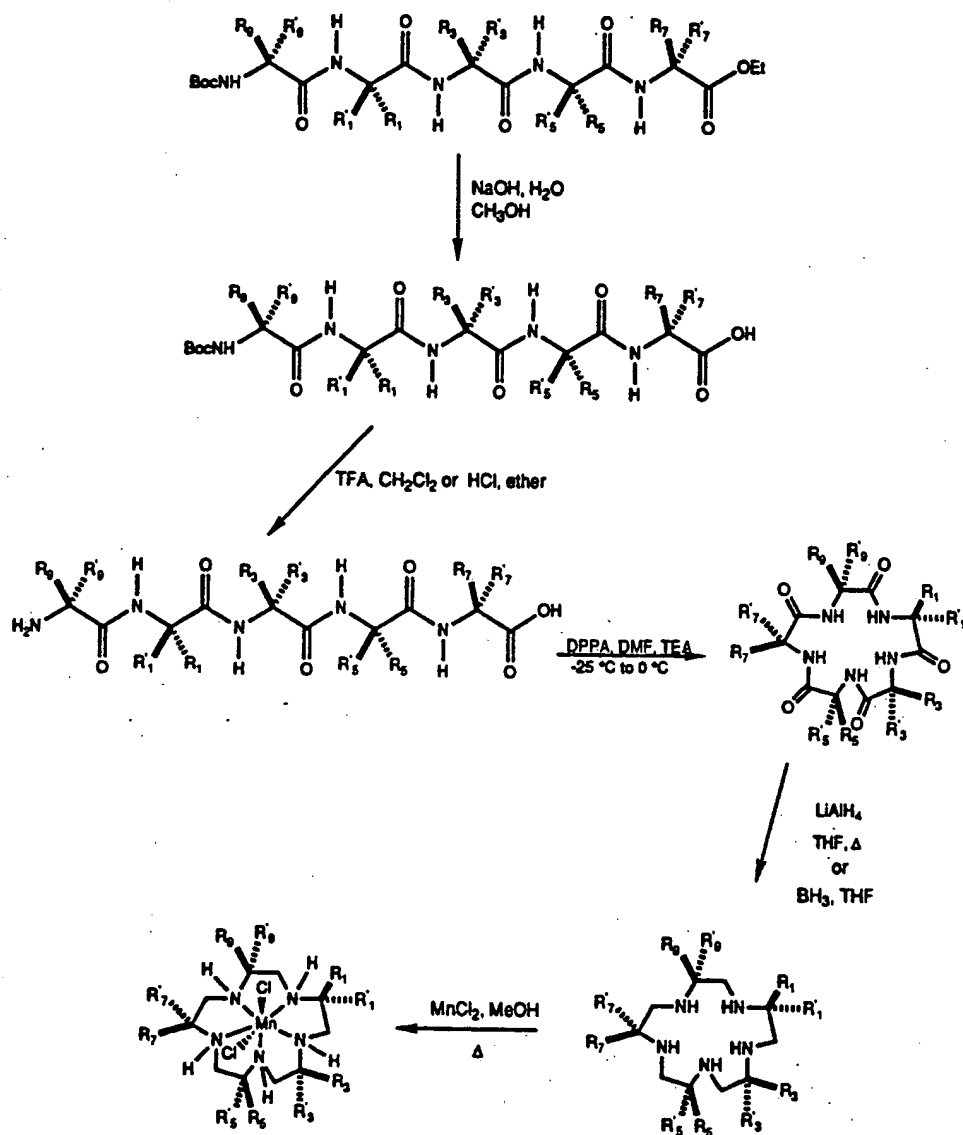
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SCHEME G
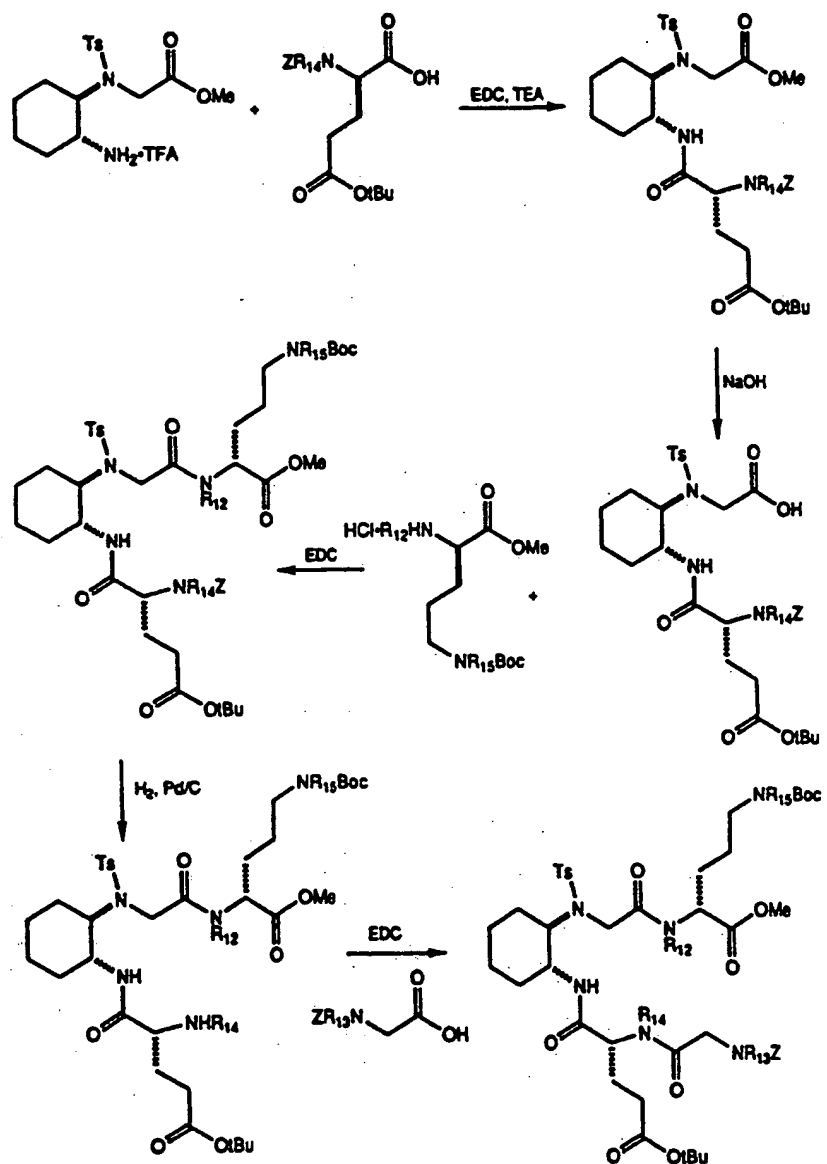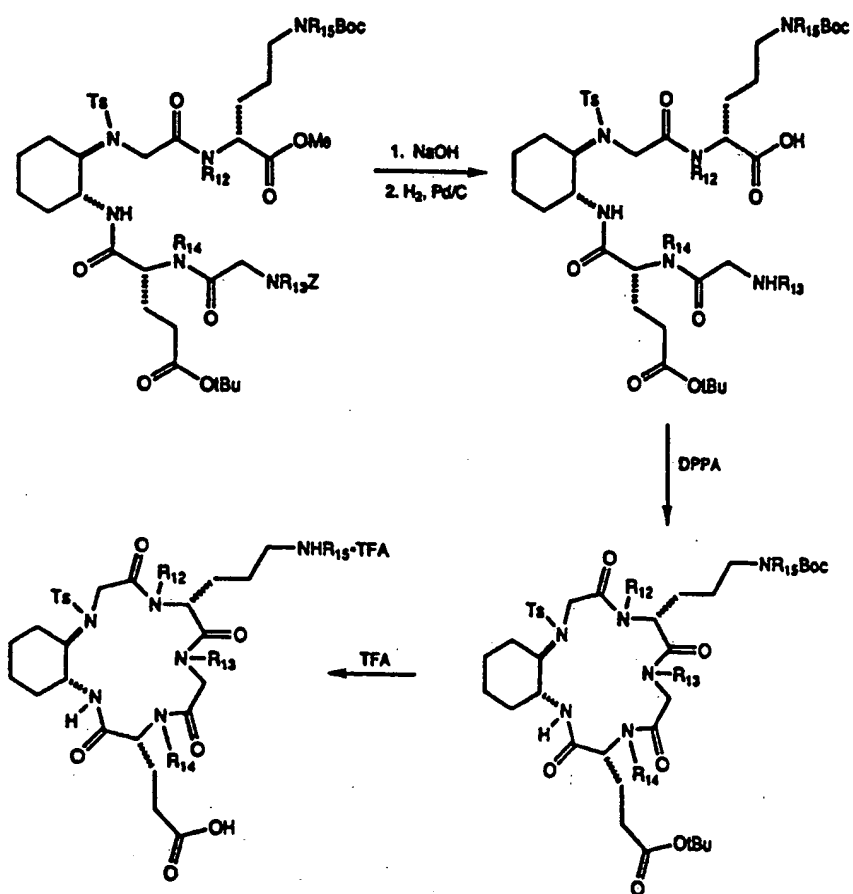
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SCHEME G (Con't.)

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SCHEME G (Con't.)

The macrocyclic ligands useful in the complexes of
the present invention, wherein nitrogen substituent R_{12}
and R_8 or R'_8 are connected to one another through a

5   "strap" or second ring system in a bicyclic sense and
R_{13}, R_{14} and R_{17} can be H or any functionality previously
described can be prepared according to the method set
forth in Scheme H below. The TFA salt of trans-(R,R)-
1,2-diaminocyclohexyl-N-tosylglycine dipeptide surrogate

10 is coupled with Z-Glu(OtBu)-OH using EDC in DMF. This
tripeptide is then saponified and coupled with N-[3-
(Boc-amino)propyl]-Gly-OMe•HCl using EDC in DMF. The
resulting tetrapeptide is then N-deprotected by
hydrogenolysis of the Z group and coupled with Z-Gly

15 again using EDC in DMF. Saponification and
hydrogenolysis affords the deprotected
pseudopentapeptide which is cyclized with DPPA. The
side chains are then deprotected in one step using TFA
and a second "strap-cyclization" is effected again with

20 DPPA as the coupling agent. Lithium aluminum hydride
reduction affords the bicyclic ligand system which is
reacted with manganese (II) chloride under essentially
anaerobic conditions to form the corresponding
functionalized manganese (II) hexaazabicycloalkane

25 complex.

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SCHEME H
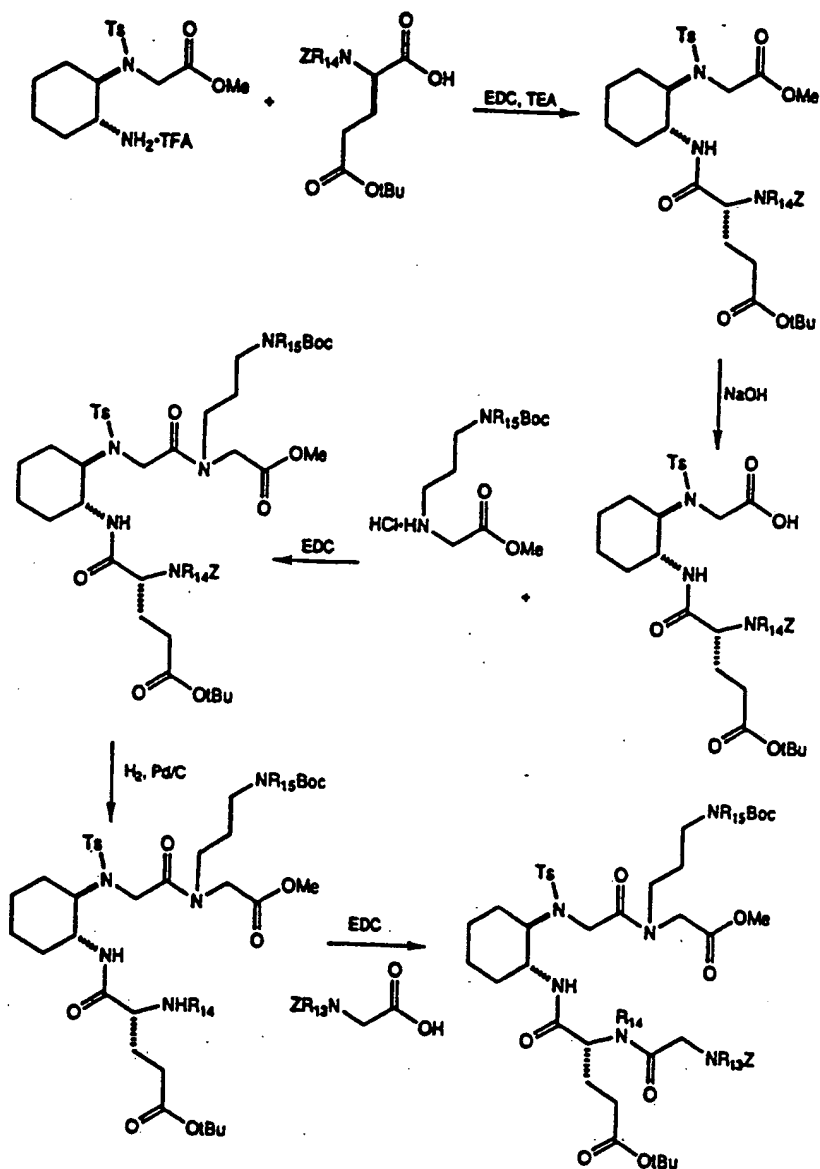
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SCHEME H (Con't.)

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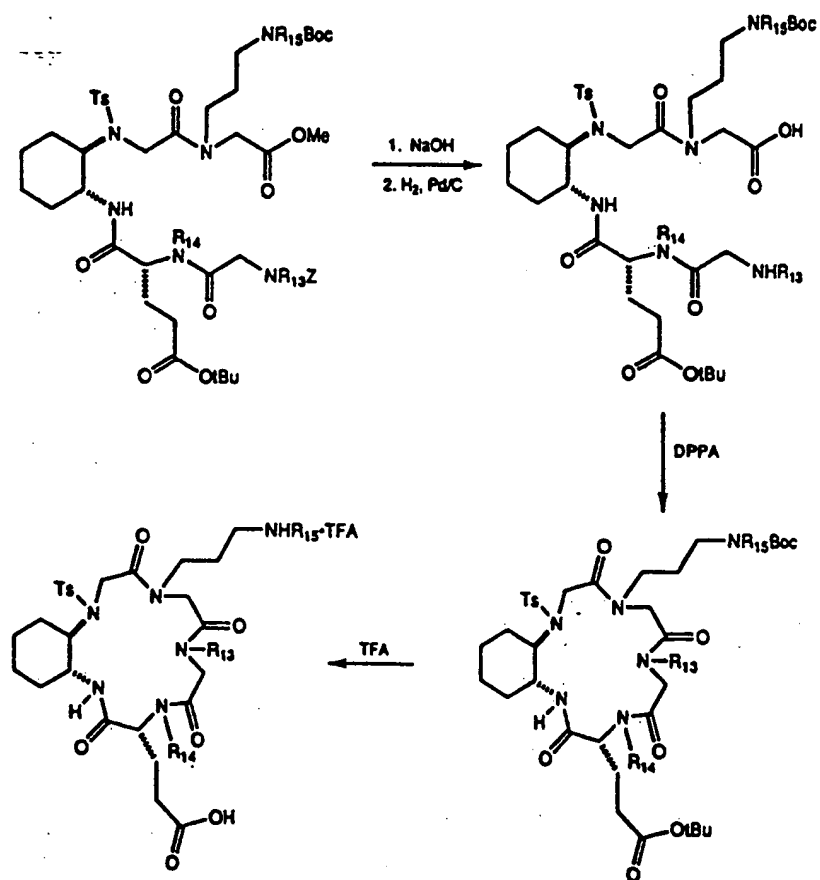
SCHEME H (Con't.)
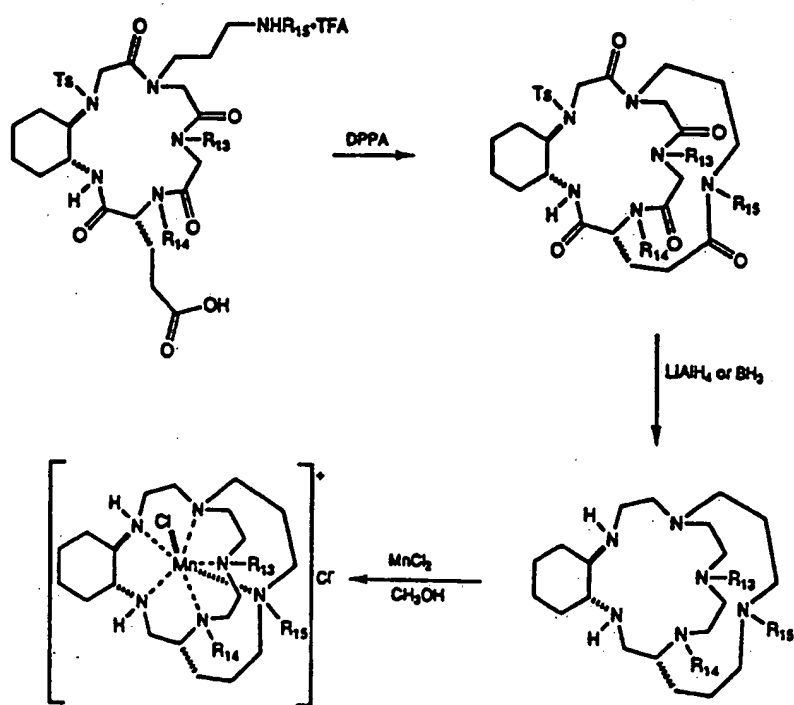
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The macrocyclic ligands useful in the complexes of
the present invention, wherein nitrogen substituents R_{12}
and R_{14} are connected to one another through a "strap" or
5 second ring system in a bicyclic sense and R_5, R'_5, R_7,
R'_7, R_9, R'_9, and R_{17} can be H or any functionality
previously described can be prepared according to the
method set forth in Scheme I below. The cyclohexyl-
containing pentaazamacrocyclic ligand, prepared
10 according to Scheme E is reacted with the ditosyl-
sulfonamide of diethanolamine, which is prepared from
diethanoamine and tosyl chloride. This "strapping"
cyclization can be conducted using Cs_2CO_3 as the base in
DMF solvent. This bicyclic ligand system is then
15 reacted with manganese (II) chloride under essentially
anaerobic conditions to form the corresponding
functionalized manganese (II) hexaazabicycloalkane
complex.

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SCHEME I
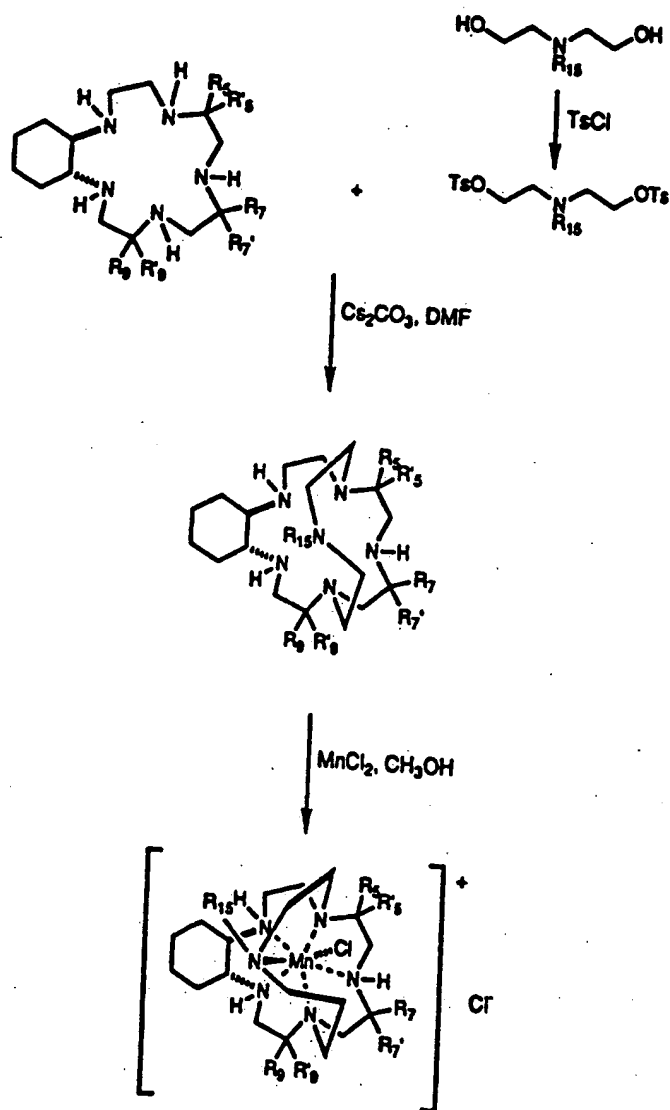
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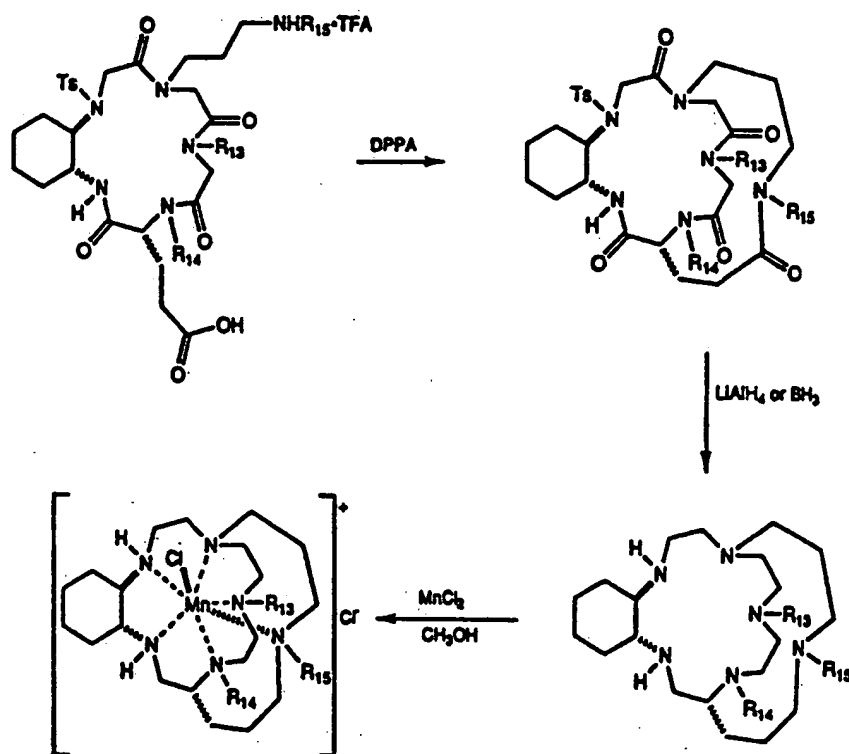The pentaazamacrocycles of the present invention
can possess one or more asymmetric carbon atoms and are
thus capable of existing in the form of optical isomers
as well as in the form of racemic or nonracemic mixtures
5   thereof. The optical isomers can be obtained by
resolution of the racemic mixtures according to
conventional processes, for example by formation of
diastereoisomeric salts by treatment with an optically
active acid. Examples of appropriate acids are
10 tartaric, diacetyltartaric, dibenzoyltartaric,
ditoluoyltartaric and camphorsulfonic acid and then
separation of the mixture of diastereoisomers by
crystallization followed by liberation of the optically
active bases from these salts. A different process for
15 separation of optical isomers involves the use of a
chiral chromatography column optimally chosen to
maximize the separation of the enantiomers. Still
another available method involves synthesis of covalent
diastereoisomeric molecules by reacting one or more
20 secondary amine group(s) of the compounds of the
invention with an optically pure acid in an activated
form or an optically pure isocyanate. The synthesized
diastereoisomers can be separated by conventional means
such as chromatography, distillation, crystallization or
25 sublimation, and then hydrolyzed to deliver the
enantiomerically pure ligand. The optically active
compounds of the invention can likewise be obtained by
utilizing optically active starting materials, such as
natural amino acids.
30   The methods of diagnostic analysis of the present
invention involve administering the complexes, i.e.
contrast enhancing agents, of the invention to a human
or non-human animal subject or host, in an amount
sufficient to effect the desired contrast (or shift) and
35 then subjecting the host to diagnostic analysis.
Preferably diagnostic analysis is NMR analysis;

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including and especially preferred, NMR imaging analysis
(or MRI). Further, the complexes of the present
invention are useful in diagnostic analysis by X-ray
image analysis, ultrasonic analysis or scintigraphic
5 analysis. While described primarily as contrast
enhancing agents, the complexes of the invention can act
as NMR shift reagents and such use is contemplated by
the methods herein.

The complexes of the invention used as contrast
10 enhancing agents are administered in an amount
sufficient to effect the desired contrast. For NMR,
this amount is an NMR signal effecting amount of the
complex, i.e. any amount of said complex that will alter
the spin-lattice, spin-spin or spin-echo relaxation
15 times of an NMR signal or for a shift reagent,
selectively shift the spectrical position of a resonance
nucleus relative to other similar nuclei. This
alteration is effected in a manner in order to enhance
the signals received from the subject under analysis
20 either by reducing the aforementioned relaxation times
or by increasing them with respect to an area of the
host or the host per se which has had the complex
administered to it. In another embodiment, the NMR
signal effecting amount of the complex is that amount
25 which in addition to changing the relaxation times of
the NMR signals in the host, will also change such
relaxation times sufficiently so that sharper lines of
definition or higher contrast is obtained between those
parts of the host that have and have not been
30 administered the complex.

The relaxation time T_1 (called the spin-lattice)
measures the rate at which magnetic energy is
transferred from the resonance nuclei to all other
energetic degrees of freedom excluding other resonance
35 nuclei. The relaxation time T_2 (spin-spin) measures the
rate of magnetization transfer to other resonance nuclei.

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Another parameter which can be measured is the density ρ of the protons in the medium. As a first approximation, it represents the quantity of free water contained in the sample.

5   The image by nuclear magnetic resonance represented the distribution of these parameters ρ, T_1, T_2 or their combination. The contrast between a given tissue and the adjacent tissues increases as a function of the tissues containing more or less water or mobile protons

10   and differing relaxation times. It is also possible to modify the contrast by varying one or more of these parameters (experimentally echoes of spins aiding the function of T_2, or reversal-recovery of the magnetization permitting the local measurement of T_1).

15   Experience has shown that it was of greater interest to modify the relaxation time to improve the contrast of the image which can be accomplished, for example, with the contrast enhancing agents provided herein. The density of the protons (in practice those of water and

20   lipids) varies little between individual organs and often less between normal and pathological tissues. However, the relaxation characteristics are dependent on a larger number of factors (microscopic dynamics of the molecules, chemical exchange, paramagnetic disturbances,

25   etc.) which are much more variable.

A detailed discussion of NMR and theoretical considerations in selecting the appropriate parameters for diagnostic analysis, e.g. MRI, is rendered in U.S. Pat. No. 4,749,560 which is incorporated herein by

30   reference. X-ray image analysis, ultrasonic diagnosis, scintigraphic image analysis and radiotherapy utilizing the complexes of the invention are all conducted in accordance with well-established techniques known to those of ordinary skill in the art.

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Moreover, the method of diagnostic analysis of the
invention allows tissue or organ-specific diagnostic
analysis to be achieved. For example, the contrast
enhancing agents can exhibit organ and tissue
5 specificity, e.g. biodifferental distribution, such as
in myocardial tissue when the complexes of the invention
are lipophilic in nature.

The complexes of the invention may be administered
to a host as a pharmaceutical composition in a contrast-
10 enhancing amount. The pharmaceutical compositions
contain a contrast-enhancing dosage of the contrast
agents according to the invention together with a
nontoxic pharmaceutically acceptable carrier, adjuvant
or vehicle. The compositions can be administered by
15 well-known routes including oral, intravenous (if
soluble), intramuscular, intranasal, intradermal,
subcutaneous, parenteral, enteral and the like.
Depending on the route of administration, the
pharmaceutical composition may require protective
20 coatings.

The pharmaceutical forms suitable for injectable
use includes sterile aqueous solutions or dispersions
and sterile powders for the extemporaneous preparation
of sterile injectable solutions or dispersions. In all
25 cases the ultimate solution form must be sterile and
fluid. Typical carriers include a solvent or dispersion
medium containing, for example, water, buffered aqueous
solutions (i.e. biocompatable buffers), ethanol, polyol
(glycerol, propylene glycol, polyethylene glycol, and
30 the like), suitable mixtures thereof, surfactants or
vegetable oils. Sterilization can be accomplished by
any art recognized technique, including but not limited
to, addition of antibacterial or antifungal agents, for
example, paraben, chlorobutanol, phenol, sorbic acid,
35 thimerosal, and the like. Further, isotonic agents,

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such as sugars or sodium chloride may be incorporated in
the subject compositions.

Production of sterile injectable solutions
containing the subject contrast agent is accomplished by
5   incorporating these agents in the required amount in the
appropriate solvent with various ingredients enumerated
above, as required, followed by sterilization,
preferably filter sterilization. To obtain a sterile
powder, the above solutions are vacuum-dried or freeze-
10   dried as necessary.

Solid dosage forms for oral administration may
include capsules, tablets, pills, powders, granules and
gels. In such solid dosage forms, the active compound
may be admixed with at least one inert diluent such as
15   sucrose, lactose or starch. Such dosage forms may also
comprise, as in normal practice, additional substances
other than inert diluent, e.g. lubricating agents such
as magnesium stearate. In the case of capsules, tablets
and pills, the dosage forms may also comprise buffering
20   agents. Tablets and pills can additionally be prepared
with enteric coatings.

Liquid dosage forms for oral administration may
include pharmaceutically acceptable emulsions,
solutions, suspensions, syrups, and elixirs containing
25   inert diluent commonly used in the art, such as water.
Such compositions may also comprise adjuvants, such as
wetting agents, emulsifying and suspending agents, and
sweetening, flavoring, and perfuming agents.

The contrast agents of the inventions are thus
30   compounded for convenient and effective administration
in pharmaceutically effective amounts with a suitable
pharmaceutically acceptable carrier, adjuvant or vehicle
in a dosage which effects contrast enhancement. These
amounts are preferably about 1 μmol to 1 mol of the
35   contrast agent per liter and/or administered in doses of
about 0.001 to 5 mmol/kg body weight. Preferred

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compositions provide effective dosages of contrast
agents in the range of about 0.001-5 mmol/kg for NMR
diagnostics, preferably about 0.005-0.5 mmol/kg; in the
range of about 0.1-5 mmol/kg for X-ray diagnostics; and
5   in the range of about 0.1-5 mmol/kg for ultrasound
diagnostics. For scintigraphic diagnostics, the dose of
the contrast agent should generally be lower than for
NMR diagnostics, e.g. MRI. For radiotherapy,
conventional doses known to those of ordinary skill in
10 the art can be used.
        As used herein, a pharmaceutically acceptable
carrier, adjuvant or vehicle includes any and all
solvents, dispersion media, coatings, antibacterial and
antifungal agents, isotonic agents, and the like. The
15 use of such media and agents are well known in the art.
        Contemplated equivalents of the general formulas
set forth above for the compounds and derivatives as
well as the intermediates are compounds otherwise
corresponding thereto and having the same general
20 properties such as tautomers of the compounds and such
as wherein one or more of the various R groups are
simple variations of the substituents as defined
therein, e.g., wherein R is a higher alkyl group than
that indicated, or where the tosyl groups are other
25 nitrogen or oxygen protecting groups or wherein the
O-tosyl is a halide. Anions having a charge other than
1, e.g., carbonate, phosphate, and hydrogen phosphate,
can be used instead of anions having a charge of 1, so
long as they do not adversely affect the overall
30 activity of the complex. However, using anions having a
charge other than 1 will result in a slight modification
of the general formula for the complex set forth above.
In addition, where a substituent is designated as, or
can be, a hydrogen, the exact chemical nature of a
35 substituent which is other than hydrogen at that
position, e.g., a hydrocarbyl radical or a halogen,

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hydroxy, amino and the like functional group, is not
critical so long as it does not adversely affect the
overall activity and/or synthesis procedure.

The chemical reactions described above are
5 generally disclosed in terms of their broadest
application to the preparation of the compounds of this
invention. Occasionally, the reactions may not be
applicable as described to each compound included within
the disclosed scope. The compounds for which this
10 occurs will be readily recognized by those skilled in
the art. In all such cases, either the reactions can be
successfully performed by conventional modifications
known to those skilled in the art, e.g., by appropriate
protection of interfering groups, by changing to
15 alternative conventional reagents, by routine
modification of reaction conditions, and the like, or
other reactions disclosed herein or otherwise
conventional, will be applicable to the preparation of
the corresponding compounds of this invention. In all
20 preparative methods, all starting materials are known or
readily preparable from known starting materials.

Without further elaboration, it is believed that
one skilled in the art can, using the preceding
description, utilize the present invention to its
25 fullest extent. The following preferred specific
embodiments are, therefore, to be construed as merely
illustrative, and not limitative of the remainder of the
disclosure in any way whatsoever.

30   EXAMPLES

All reagents were used as received without
purification unless otherwise indicated. All NMR
spectra were obtained on a Varian VXR-300 or VXR-400
35 nuclear magnetic resonance spectrometer. Qualitative
and quantitative mass spectroscopy was run on a Finnigan

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MAT90, a Finnigan 4500 and a VG40-250T using m-
nitrobenzyl alcohol(NBA) or m-nitrobenzyl alcohol/LiCl
(NBA+Li). Melting points (mp) are uncorrected.

5   The following abbreviations relating to amino acids
and their protective groups are in accordance with the
recommendation by IUPAC-IUB Commission on Biochemical
Nomenclature (Biochemistry, 11, 1726 (1972)) and common
usage.

Ala	L-Alanine
10 DAla	D-Alanine
Gly	Glycine
Ser	L-Serine
DSer	D-Serine
Ppg	Propargylglycine
15 Tyr	L-Tyrosine
Bzl	Benzyl
Boc	tert-Butoxycarbonyl
Et	Ethyl
TFA	Trifluoroacetate
20 DMF	Dimethylformamide
HOBT•H_2O	1-Hydroxy-(1H)-benzotriazole monohydrate
EDC•HCl	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
25 TEA	Triethylamine
DMSO	Dimethylsulfoxide
THF	Tetrahydrofuran
DPPA	Diphenylphosphoryl azide
DMPU	Dimethylpropyleneurea
30 c	concentration, g/cc
DME	1,2-Dimethoxyethane

The abbreviation Cyc represents 1,2-
cyclohexanediamine (stereochemistry, i.e. R,R or S,S, is
35 indicated as such). This allows three letter code

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peptide nomenclature to be used in pseudopeptides
containing the 1,2-cyclohexane diamine *residue*.

Example 1 (Comparative)
5 A. Synthesis of 1,4,7-Tris(p-toluenesulfonyl)-1,4,7-
triazaheptane

This compound was synthesized following the
procedure of Atkins, T. J.; Richman, J.E.; and
10 Oettle, W.F.; *Org. Synth.*, 58, 86-98 (1978). To a
stirred solution of p-toluenesulfonyl chloride (618 g,
3.24 mole) in pyridine (1500 ml) at 0°C was added a
solution of 1,4,7-triazaheptane (95.5 g, 0.926 mole) in
pyridine (150 ml) under a dry argon atmosphere,
15 maintaining the temperature ≤ 50°C. The addition
required 30 minutes. After the mixture was allowed to
cool to room temperature slowly while stirring for 3 h,
H_2O(2 l) was slowly added to the cooled (ice bath)
mixture. The heavy white precipitate which formed was
20 filtered and washed thoroughly with H_2O. The pale
yellow solid was dissolved in DMF (3 l) and 0.1 N HCl (4
l) was slowly added at 5°C. The slurry was filtered and
the pale yellow solid was washed thoroughly with H_2O and
dried in vacuo to give 486 g (93% yield) of the product:
25 mp 180-1°C; ^1H NMR(DMSO-d_6) δ 2.39 (s,3 H), 2.40 (s, 6
H), 2.84 (m, 4 H), 3.04 (t, J=6.9 Hz, 4 H) 7.40 (d,
J=8.1 Hz, 4 H), 7.59 (d, J=8.3 Hz, 2 H), 7.67 (m, 6 H).
B. Synthesis of 1,4,7-Tris(p-toluenesulfonyl)-1,4,7-
triazaheptane-1,7-disodium Salt
30   This compound was synthesized following the
procedure of Atkins, T.J.; Richman, J.E., and Oettle,
W.F.; *Org. Synth.*, 58 86-98 (1978). To a mechanically
stirred slurry of 1,4,7-tris(p-toluenesulfonyl)-1,4,7-
triazaheptane prepared as in Example 1A (486 g, 0.859
35 mole) in ethanol (1150 ml) heated to reflux under a dry
argon atmosphere was added a solution of sodium ethoxide

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(prepared by dissolving sodium metal (39.5 g, 1.72 mole)
in absolute ethanol (1.0 l)) as rapidly as possible.
The clear brown solution which formed rapidly was
allowed to cool to room temperature and ethyl ether (1.0
5   l) was added. The crystals were filtered under a dry
argon blanket, washed with 3:1 ethanol:ethyl ether and
ethyl ether. The crystals were then dried in vacuo to
give 509 g (97% yield) of the product as a white powder:
^{1}H NMR (DMSO-d_6) δ 2.30 (s 6 H), 2.36 (s, 3 H), 2.63 (t,
10   J=8.7 Hz, 4 H), 2.89 (t, J=7.2 Hz, 4 H) 7.11 (d, J=8.1
Hz, 4 H), 7.28 (d, J=8.0 Hz, 2 H), 7.46 (m, 6 H).
C. Synthesis of 3,6-Bis(p-toluenesulfonyl)-3,6-
diazaoctane-1,8-di-p-toluenesulfonate

To a stirred solution of p-toluenesulfonyl chloride
15   (566 g, 2.97 mole) and triethylamine (300 g, 2.97 mole)
in CH_2Cl_2 (2.0 l) at 0°C under a dry argon atmosphere was
added 3,6-diazaoctane-1,8-diol (100 g, 0.675 mole) in
portions, maintaining the temperature <10°C. The
addition required 30 minutes. The mixture was allowed
20   to warm to room temperature while stirring an additional
18 h and was then poured onto ice (1000 g). The CH_2Cl_2
layer was separated, washed with 10% HCl, H_2O and
saturated NaCl solution, and dried ($MgSO_4$). The
solution was concentrated in vacuo to a volume of 1.5 l.
25   Crystallization by the addition of hexane (4 l) gave 477
g (92% yield) of the product as colorless needles: mp
151-3°C; ^{1}H NMR (CDCl$_3$) δ 2.43 (s, 12 H), 3.29 (s, 4 H),
3.36 (t, J=5.2 Hz, 4 H) 4.14 (t, J=5.2 Hz, 4 H), 7.33
(d, J=7.8 Hz, 8 H), 7.71 (d, J=8.2 Hz, 4 H), 7.79 (d,
30   J=8.3 Hz, 4 H).
D. Synthesis of 1,4,7,10,13-Penta(p-toluenesulfonyl)-
1,4,7,10,13-pentaazacyclopentadecane

This compound was synthesized following the
procedure of Richman, J.E., and Atkins, T.J., J. Am.
35   Chem. Soc., 96, 2268-70 (1974). To a stirred solution
of 1,4,7-tris(p-toluenesulfonyl)-1,4,7-triazaheptane-

1,7-disodium salt prepared as in Example 1B (146 g,
0.240 mole) in anhydrous DMF (2250 ml) was added
dropwise over 3 h to a solution of 3,6-bis(p-toluene-
sulfonyl)-3,6-diazaoctane-1,8-di-p-toluenesulfonate
5 prepared as in Example 1C (184 g, 0.240 mole) in
anhydrous DMF (1020 ml) under a dry argon atmosphere,
maintaining the temperature at 100°C. After stirring an
additional 1 h at 100°C, the solution was concentrated
in vacuo to a volume of 1.5 l. H_2O (500 ml) was slowly
10 added at 80°C to crystallize the product. The resulting
slurry was slowly cooled to 0°C and additional H_2O (1250
ml) added. The solid was filtered, washed thoroughly
with H_2O and then 90% ethanol and dried in vacuo. The
off-white solid was dissolved in CH_2Cl_2, insoluble
15 impurities were removed by filtration and the filtrate
was washed with H_2O and then dried ($MgSO_4$). The solvent
was removed in vacuo to give a yellow solid which was
purified by recrystallization from CH_2Cl_2-hexane to give
164 g (69% yield) of the product as a white crystalline
20 solid: mp 290-3°C; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 15 H) 3.27
(s, 20 H), 7.32 (d, J=8.3 Hz, 10 H), 7.66 (d, J=8.3 Hz,
10 H).

E. Synthesis of 1,4,7,10,13-Pentaazacyclopentadecane
        A mixture of 1,4,7,10,13-penta(p-toluenesulfonyl)-
25 1,4,7,10,13-pentaazacyclopentadecane prepared as in
Example 1D (168 g, 0.170 mole) and concentrated H_2SO_4
(500 ml) was heated at 100°C with stirring under a dry
argon atmosphere for 70 h. To the resulting dark brown
solution ethanol (500 ml) was added dropwise with
30 stirring at 0°C followed by ethyl ether (3 l). The
white solid was filtered and washed with ethyl ether.
The solid was then dissolved in H_2O (500 ml) and the
resulting solution washed with ethyl ether. Upon
reducing the volume of the solution in vacuo to 200 ml,
35 the pH was adjusted to 10-11 with 10 N NaOH and the
solvent was removed in vacuo. Ethanol (500 ml) was then

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added and removed in vacuo to dryness. The resulting
tan oily solid was extracted with hot THF (2x500 ml) and
filtered at room temperature. The filtrates were
combined and the solvent removed in vacuo to give the
5 crude product as a yellow crystalline solid which was
then redissolved in CH$_3$CN and filtered to remove
insoluble impurities. Recrystallization from cold
(-20°C) CH$_3$CN gave 11.3 g (31% yield) of the product as
colorless needles: mp 108-9°C; ^{1}H NMR (CDCl$_3$) δ 1.74 (br
10 s, 5 H), 2.73 (s, 20 H); Exact mass (M+Li)$^+$: calcd,
222.2270; Found, 222.2269 (C$_{10}$H$_{25}$N$_5$Li).
F. Synthesis of [Manganese(II)dichloro(1,4,7,10,13-
Pentaazacyclopentadecane)]

    A solution of 1,4,7,10,13-pentaazacyclopentadecane
15 prepared as in Example 1E (2.0 g, 9.3 mmole) and
anhydrous manganese(II) chloride (1.2 g, 9.3 mmole) in
anhydrous methanol (50 ml) was refluxed under a dry
nitrogen atmosphere for 3 h. The solution was filtered
and the solvent removed in vacuo. The resulting solid
20 was recrystallized from ethanol-ethyl ether to give 2.79
g (88% yield) of the product as an off-white crystalline
solid: FAB mass spectrum (NBA) m/z (relative intensity)
340 (M$^+$, 2), 305/307 ((M-Cl)$^+$ 100/45)); Anal. Calcd. for
C$_{10}$H$_{25}$Cl$_2$MnN$_5$: C, 35.17; H, 7.38; Cl, 20.76; N 20.60.
25 Found: C, 34.95; H, 7.31; Cl, 20.49; N, 20.22.

                        Example 2

A. Synthesis of Dimethyl 3,6,9-Tris(p-toluenesulfonyl)-
30 3,6,9-triazaundecanedioate
    1,4,7-Tris(p-toluenesulfonyl)-1,4,7-triazaheptane-
1,7-disodium salt prepared as in Example 1B (30 g, 49.2
mmol) was dissolved in dry N,N-dimethylformamide (180
ml) under argon. After cooling to 0° C in an ice bath,
35 methyl chloroacetate (15.40 g, 141.9 mmol) was added
dropwise over a 10 min period. The reaction mixture

became cloudy at the end of the addition, and was
allowed to stir overnight while the ice bath warmed to
room temperature. The solvent was evaporated under
reduced pressure to give a brown oil which was dissolved
5 in ethyl acetate (450 ml) giving a milky solution. This
solution was washed twice with water (500 ml, then 300
ml). The combined water layers were back extracted with
ethyl acetate (300 ml). The combined ethyl acetate
layers were washed twice with saturated sodium chloride
10 solution (200 ml), filtered, and evaporated to dryness.
This residue was dissolved in dichloromethane (200 ml)
and evaporated to dryness, and placed on the vacuum
line. After recrystallization from chloroform-methanol,
and washing with methanol and ether, an off-white solid
15 was obtained weighing 27.46 g. An additional quantity
of a slightly darker solid (4.7 g) was recovered from
the filtrate after removing the solvent and
recrystallizing as before. Total yield was 32.2 g (93%
yield): mp 141-2° C; ^{1}H NMR (CDCl$_3$) δ 2.42 and 2.44 (2
20 s, 9 H), 3.41 (br s, 8 H), 3.60 (s, 6 H), 4.07 (s, 4 H),
7.26 - 7.35 (m, 6 H), 7.63 - 7.74 (m, 6 H).
    B. Synthesis of 3,6,9-Tris(p-toluenesulfonyl)-3,6,9-
triazaundecanedioic Acid

        Dimethyl 3,6,9-tris(p-toluenesulfonyl)-3,6,9-
25 triazaundecanedioate prepared as in Example 2A (16 g,
22.5 mmol) was slurried in tetrahydrofuran (100 ml).
Sodium hydroxide (2 N, 160 ml) was added dropwise over a
1 h period. After 72 h, the solvent was evaporated
under reduced pressure, and hydrochloric acid (1 N) was
30 added to lower the pH to 4. This aqueous phase was
extracted several times with ethyl acetate. The
combined ethyl acetate layers were washed twice with
brine, dried (MgSO$_4$), filtered, and evaporated to give a
white solid, 14.22 g (93% yield): mp 177-80° C; ^{1}H NMR
35 (DMSO-d$_6$) δ 2.38 and 2.40 (2 s, 9 H), 3.10 (m, 4 H),
3.29 (m, 4 H), 3.73 (s, 4 H), 7.37 and 7.41 (2 d, J =

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7.9, 8.2 Hz, 6 H), 7.61 and 7.66 (2 d, J = 8.2 , 8.0 Hz, 6 H).

C.   Synthesis of 3,6,9-Tris(p-toluenesulfonyl)-3,6,9-triazaundecanedioyl Dichloride

3,6,9-Tris(p-toluenesulfonyl)-3,6,9-triazaundecanedioic acid prepared as in Example 2B (40.5 g, 59.4 mmol) was placed in a round bottom flask under argon, and oxalyl chloride (400 g, 3.15 moles) was added. This mixture, initially cloudy, became clear after a few hours, and was stirred overnight at room temperature. At the end of this time it was heated to 40 C for 30 min. Oxalyl chloride was removed on the rotary evaporator. Dichloromethane (50 to 60 ml) was added to dissolve the resulting solid, and was removed on the rotary evaporator. This process was repeated twice, giving 40.5 g (99% yield) of a white solid: mp 136-7 C; ^{1}H NMR (CDCl$_3$) δ 2.43 and 2.46 (2 s, 9 H), 3.30 - 3.38 (m, 4 H), 3.40 - 3.48 (m, 4 H), 4.56 (s, 4 H), 7.30 - 7.40 (m, 6 H), 7.71 (d, J = 8.2 Hz, 6 H).

D.   Synthesis of trans-5,6-Cyclohexano-1,10,13-tris(p-toluenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecan-3,8-dione

Dry dichloromethane (150 ml) was placed in a one liter four necked round bottom flask under argon equipped with two dropping funnels. 3,6,9-Tris(p-toluenesulfonyl)-3,6,9-triazaundecanedioyl dichloride prepared as in Example 2C (5.07 g, 7.05 mmol) was dissolved in dry dichloromethane (150 ml) and added to one of the dropping funnels. trans-1,2-Diaminocyclohexane (0.805 g, 7.05 mmol) and triethylamine (1.96 ml, 14.1 mmol) were dissolved in dry dichloromethane (150 ml) and added to the other dropping funnel. After cooling the dichloromethane containing flask in an ice bath to an internal temperature of 0 to 5 C, the contents of the dropping funnels were added

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simultaneously to the stirred solution over 2.25 h. A
white precipitate was evident before the addition was
finished. At the end of this time, the ice bath was
removed and the reaction mixture was stirred overnight
5 at room temperature. The reaction mixture was filtered
and the white precipitate was identified as pure
product. The filtrate was washed twice with water (100
ml), once with saturated sodium chloride solution (100
ml), dried ($MgSO_4$), filtered, and the solvent was
10 removed under reduced pressure. Recrystallization from
dichloromethane-hexane provided additional product,
along with the initial precipitate for a total of 2.85 g
(53% yield); mp 254-5 C; ^1H NMR (DMSO-d_6) δ 1.15 (br
s, 4 H), 1.52 - 1.75 (m, 4 H), 2.42 and 2.43 (2 s, 9 H),
15 3.04 (m, 8 H), 3.51 (d + m, J = 16.5 Hz, 4 H), 4.01 (d,
J = 16.5 Hz, 2 H), 7.35 - 7.53 (m, 8 H), 7.71 (d, J =
8.3 Hz, 4 H), 7.80 (br d, J = 10.5 Hz, 2 H).

E.   Synthesis of trans-1,2-
20 Bis(chloroacetamido)cyclohexane
        A 12 liter three-neck flask equipped with a
magnetic stirbar and two 1 liter dropping funnels was
charged with 1,2-diaminocyclohexane (35.0 g, 0.310 mol)
dissolved in chloroform (375 ml) and water (185 ml).
25 The two dropping funnels were charged individually with
chloroacetyl chloride (75 ml, 0.94 mol) in chloroform
(440 ml) and potassium carbonate (120.5 g, 0.87 mol) in
water (4 1), added in four portions during the addition.
The flask was cooled in an ice salt bath and addition of
30 the reagents was carried out over 2 h. The ice salt
bath was removed, water (600 ml) was added, and the
reaction mixture was stirred for 2.5 h. The mixture was
separated and the water layer was extracted with
chloroform several times. The combined chloroform
35 layers were washed with water and then brine. The
organic layer was dried (sodium sulfate) and

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concentrated in vacuo to yield an off-white solid. The
solid was washed with ether to yield 55.32 g (67% yield)
of a white solid after drying in vacuo: mp 202-3 C; ^{1}H
NMR (CDCl$_3$) δ 1.27 - 1.50 (m, 4 H), 1.75 - 1.95 (m, 2
5 H), 2.03 - 2.20 (m, 2 H), 3.72 - 3.87 (m, 2 H), 4.05 (s,
4 H), 6.81 (br s, 2 H).

F.   Synthesis of trans-5,6-Cyclohexano-1,10,13-tris(p-
toluenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecan-
10 3,8-dione (alternate method)
          A 5 liter three-neck flask equipped with a
magnetic stir bar and 1 liter dropping funnel was dried
and placed under a dry argon atmosphere. A solution of
trans-1,2-bis(chloroacetamido)cyclohexane prepared as in
15 Example 2E (6.68 g, 250 mmol) in anhydrous DMF (1.25 l)
was added to a solution of 1,4,7-tris(p-
toluenesulfonyl)-1,4,7-triazaheptane-1,7-disodium salt
prepared as in Example 1B (15.2 g, 250 mmol) in
anhydrous DMF (1.25 l) at room temperature over a period
20 of 12 h. After stirring an additional 2 h, the solvent
was removed in vacuo. The solid residue was triturated
with chloroform (1 l) and filtered to yield a white
solid. The solid was recrystallized from acetonitrile
to give 7.22 g (38% yield) of fluffy white crystals: mp
25 254-5 C; ^{1}H NMR (DMSO-d$_6$) δ 1.15 (br s, 4 H), 1.52 -
1.75 (m, 4 H), 2.42 and 2.43 (2 s, 9 H), 3.04 (m, 8 H),
3.51 (d + m, J = 16.5 Hz, 4 H), 4.01 (d, J = 16.5 Hz, 2
H), 7.35 - 7.53 (m, 8 H), 7.71 (d, J = 8.3 Hz, 4 H),
7.80 (br d, J = 10.5 Hz, 2 H).
30 G.   Synthesis of trans-2,3-Cyclohexano-1,4,7,10,13-
pentaazacyclopentadecane
          trans-5,6-Cyclohexano-1,10,13-tris(p-
toluenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecan-
3,8-dione prepared as in Example 2D (1.765 g, 2.32 mmol)
35 was suspended in 1,2-dimethoxyethane (dme, 40 ml) under
argon, and the flask was placed in a water bath.

Lithium aluminum hydride (0.5 M in dme, 55 ml, 27.5
mmol) was added over a 5 min period. Five min later
heating with a mantle was started, and reflux began 15
min later. The reaction became almost colorless after a

5 few min of reflux, later turning yellow with white
precipitate. Reflux was continued for 43.5 h, and then
the reaction mixture was allowed to cool to room
temperature. The reaction was quenched by the careful
addition of water (0.86 ml) using a water bath for

10 cooling. Five min later, 15% aqueous sodium hydroxide
solution (0.86 ml) was added followed by water (2.6 ml).
The slight yellowish color largely discharged during
this process. One h later, tetrahydrofuran (55 ml) was
added and stirring was continued for 2 h. The quenched

15 reaction mixture was filtered. The filtrate was
evaporated under reduced pressure and placed on the
vacuum line, giving a yellowish-white solid. This solid
was dissolved in dichloromethane and filtered, then
concentrated to a solid and placed on the vacuum line.

20 It was recrystallized from hot acetonitrile under argon,
producing 0.316 g (50% yield) of white needles : mp
112-3 C (under nitrogen); ^{1}H NMR (CDCl$_3$) δ 0.97 (m, 2
H), 1.22 (m, 2H), 1.39 - 1.96 (3 m, 7 H), 2.11 (m, 4 H),
2.49 (m, 2 H), 2.54 - 2.88 (several m, 12 H), 2.94 (m, 2

25 H); Exact mass (M + H)$^+$: calcd, 270.2658; found,
270.2658 (C$_{14}$H$_{32}$N$_5$).

H. Synthesis of [Manganese(II)dichloro(trans-2,3-
Cyclohexano-1,4,7,10,13-pentaazacyclopentadecane)]
       trans-2,3-Cyclohexano-1,4,7,10,13-

30 pentaazacyclopentadecane prepared as in Example 2G (301
mg, 1.12 mmol) was added to a hot anhydrous MeOH
solution (50 ml) containing anhydrous manganese(II)
chloride (140 mg, 1.12 mmol) under a dry nitrogen
atmosphere. After refluxing for 2 h, the solution was

35 stirred overnight at room temperature and was then taken
to dryness. The white solid was dissolved in warm

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acetone (15 ml) and the solution was filtered. The
solution was stripped to dryness and the white solid was
washed with ethyl ether. The solid was dried in vacuo
to give 0.36 g (82% yield) of product: FAB mass
5   spectrum (NBA) m/z (relative intensity) 394 (M^+, 1),
359/361 [$(M-Cl)^+$, 100/29]; Anal. calcd. for
$C_{14}H_{31}N_5MnCl_2$: C, 42.54; H, 7.91; N, 17.72. Found: C,
42.56; H, 8.17; N, 17.42.

10   Example 3

A. Synthesis of Boc-DAla-Ala-OEt
     To a solution of Boc-DAla (25.0 g, 132.1 mmol) in DMF
     (1450 ml) was added HOBT•H_2O (19.8 g, 129.3 mmol) and
15   EDC•HCl (28.0 g, 146.3 mmol) and the resulting solution
     was allowed to stir at RT for 30 min. To this solution
     was added Alanine ethyl ester hydrochloride (20.3 g,
     132.1 mmol) and TEA (20.4 ml, 146.3 mmol) and the
     reaction was allowed to stir for 3 days (for
20   convenience). The DMF was evaporated and the residue
     was partitioned between water (500 ml) and ethyl acetate
     (500 ml). The ethyl acetate solution was washed with 1N
     $NaHSO_4$ (250 ml), water (250 ml), saturated $NaHCO_3$ (250
     ml), brine (250 ml) and dried over Na_2SO_4. Filtration
25   and concentration afforded 31.7 g (83 % yield) of the
     desired dipeptide as a white foam: ^1H NMR (DMSO-d_6) δ
     1.14 (d, J = 7.4 Hz, 3 H), 1.16 (t, J = 7.4 Hz, 3 H),
     1.24 (d, J = 7.0 Hz, 3 H), 1.36 (s, 9 H), 3.96 - 4.09
     (m, 3 H), 4.17 - 4.22 (apparent quintet, J = 7.4 Hz, 1
30   H), 6.77 (d, J = 7.7 Hz, 1 H), 8.09 (d, J = 7.0 Hz, 1
     H); MS (LRCI, CH_4) m/z (relative intensity) = 317 (5)
     [M + C_2H_5]$^+$, 289 (60) [M + H]$^+$.

B. Synthesis of Boc-Ala-Ala-OH
35   To a suspension of the dipeptide (15.0 g, 93.6 mmol) in
     THF (192 ml) was added 0.5 N NaOH solution (192 ml). To

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the resulting solution was added di-t-butyldicarbonate
(26.6 g, 121.7 mmol) at once. The pH of the reaction
was maintained at ~10 for 5 h and the mixture was then
allowed to stir overnite. The pH of the reaction was
5   again adjusted to ~10 and the solution was extracted
with ethyl acetate (2 x 100 ml). The pH of the aqueous
layer was adjusted to ~3.5 with aqueous potassium
bisulfate and this mixture was extracted with ethyl
acetate (3 x 100 ml). The combined extracts were dried
10   (MgSO$_4$), filtered and concentrated to afford 20.7 g (85
% yield) of the desired product as a white powder: ^{1}H
NMR (DMSO-d$_6$) δ 1.16 (d, J = 6.8 Hz, 3 H), 1.28 (d,
J = 7.3 Hz, 3 H), 1.38 (s, 9 H), 3.95 - 4.09 (m, 1 H),
4.20 (quintet, J = 7.3 Hz, 1 H), 6.87 (d, J = 8.0 Hz, 1
15   H), 8.00 (d, 7.3 Hz, 1 H); MS (HRFAB, NBA - Li) m/z =
267.1557 [M + Li]+; 267.1532 calcd for C$_{11}$H$_{20}$N$_2$O$_5$Li.

C.   Synthesis of DAla-Ala-OEt·TFA
The protected dipeptide (31.4 g, 109 mmol) was dissolved
20   in methylene chloride (200 ml) and TFA (66 ml) was
added. The resulting solution was allowed to stir for
30 min at RT and concentrated. The residue was
coevaporated with methylene chloride (2 x 200 ml),
dissoved in ether and oiled out with the addition of
25   excess hexanes. The solvents were decanted and the
residue was pumped at high vacuum for 12 h to afford
39.6 g (100 % yield, contains residual TFA) of the
desired TFA salt as an orange oil: ^{1}H NMR (DMSO-d$_6$)
δ 1.16 (t, J = 7.0 Hz, 3 H), 1.28 (d, J = 7.0 Hz, 3 H),
30   1.34 (d, J = 7.0 Hz, 3 H), 3.86 (bs, 1H), 4.07 (q, J =
7.0 Hz, 2 H), 4.26 (quintet, J = 7.0 Hz, 1 H), 8.21 (bs,
3 H), 8.86 (d, J = 7.4 Hz, 1 H); MS (LRCI, CH$_4$) m/z
(relative intensity) 217 (5) [M + C$_2$H$_5$]$^+$, 189 (40)
[M+H]$^+$.
35

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D.   Synthesis of Boc-Ala-Ala-DAla-Ala-OEt

To a solution of Boc-Ala-Ala-OH (20.1 g, 77.2 mmol) in
DMF (850 ml) was added HOBT•H₂O (13.1 g, 85.4 mmol) and
EDC•HCl (16.4 g, 85.4 mmol). To this solution was added

5 DAla-Ala-OEt•TFA (23.3 g, 77.2 mmol) followed by TEA
(11.9 ml, 85.4 mmol) and the resulting mixture was
stirred for 12 h thereafter. The DMF was evaporated and
the residue was dissolved in ethyl acetate (300 ml) and
washed with 1 N potassium bisulfate (150 ml), water (150

10 ml), saturated sodium bicarbonate (150 ml) and brine
(150 ml). The ethyl acetate layer was dried (MgSO₄),
filtered and concentrated to half volume and
crystallization was allowed to proceed. Isolation by
filtration afforded 20.5 g (62 % yield) of the desired

15 tetrapeptide as a white solid: ¹H NMR (DMSO-d₆) δ 1.13
(d, J = 7.0 Hz, 3 H), 1.17 (two coincidental d, J = 7.0
Hz, 6 H), 1.25 (d, J = 7.4 Hz, 3 H), 3.91 - 4.30 (m, 6
H), 6.87 (d , 7.0 Hz, 1 H), 7.92 (d, J = 6.3 Hz, 1 H),
8.07 (d, J = 7.3 Hz, 1 H), 8.09 (d, J = 6.6 Hz, 1 H);

20 MS (HRFAB, NBA - Li) m/z = 437.2600 [M + Li]⁺; 437.2588
calcd for C₁₉H₃₄N₄O₇Li.

E.   Synthesis of Boc-Ala-Ala-DAla-Ala-OH

A solution of Boc-Ala-Ala-DAla-Ala-OEt (10.9 g, 25.3

25 mmol) in methanol (100 ml) was treated with 2.5 M sodium
hydroxide (20.0 ml, 50.0 mmol) and the resulting
solution was allowed to stir for 2 h at RT. At this
time the pH of the solution was lowered to ~3 with the
addition of aqueous potassium bisulfate and the

30 resulting mixture was extracted with ethyl acetate (3 x
100 ml). The combined extracts were dried (MgSO₄),
filtered and concentrated to afford 6.8 g (67 % yield of
the desired acid as a white solid: ¹H NMR (DMSO-d₆) δ
1.17 (d, J = 7.2 Hz, 3 H), 1.20 (two coincidental d, J =

35 7.1 Hz, 6 H), 1.28 (d, J = 1.3 Hz, 3 H), 1.38 (s, 9 H),
3.90 - 4.00 (m, 1 H), 4.17 - 4.30 (m, 3 H), 6.93 (d, J =

6.7 Hz, 1 H), 7.96 (d, J = 6.7 Hz, 1 H), 8.04 (d, J = 7.4 Hz, 1 H), 8.07 (d, J = 7.8 Hz, 1 H); MS (HRFAB, NBA - Li) m/z = 409.2331 [M + Li]$^+$; 409.2353 calcd for $C_{17}H_{30}N_4O_7Li$.

5

F. Synthesis of Boc-Ala-Ala-DAla-Ala-DAla-OBzl
To a solution of Boc-Ala-Ala-DAla-Ala-OH (6.5 g, 16.3 mmol) in DMF (180 ml) was added HOBT•H$_2$O (2.86 g, 18.7 mmol) and EDC•HCl (3.58 g, 18.7 mmol). The resulting
10 solution was allowed to stir for 15 min at RT and treated with DAla-OBzl p-toluenesulfonate salt (6.57 g, 18.7 mmol) and TEA (2.6 ml, 18.7 mmol). This mixture was allowed to stir for 12 h thereafter. The DMF was evaporated and the residue was partitioned between ethyl
15 acetate (300 ml) and water (300 ml). The ethyl acetate layer was washed with 1 N potassium bisulfate (150 ml), water (150 ml), saturated sodium bicarbonate (150 ml) and brine (150 ml). The ethyl acetate layer was then dried (MgSO$_4$), filtered and concentrated to afford 9.0 g
20 (100 % yield) of the desired compound as a white powder: ^{1}H NMR (DMSO-d$_6$) δ 1.17 (d, J = 7.3 Hz, 3 H), 1.21 (two conincidental d, J = 7.0 Hz, 6 H), 1.22 (d, J = 7.0 Hz, 3 H), 1.32 (d, J = 7.3 Hz, 3 H), 1.37 (s, 9 H), 3.90 - 4.09 (m, 1 H), 4.18 - 4.34 (m, 4 H), 5.13 (ABq, J =
25 12.7, Δ^v = 10.5 Hz, 2 H), 6.94 (d, J = 7.3 Hz, 1 H), 7.30 - 7.41 (m, 5 H), 7.97 (d, J = 7.0 Hz, 1 H), 8.10 - 8.18 (m, 2 H), 8.25 (d, J = 6.9 Hz, 1 H); MS (HRFAB, NBA - Li) m/z = 570.3140 [M + Li]$^+$; 570.3115 calcd for $C_{27}H_{41}N_5O_8Li$.

30

G. Synthesis of Ala-Ala-DAla-Ala-DAla•HCl
Boc-Ala-Ala-DAla-Ala-DAla-OEt (10.4 g, 18.7 mmol) was dissolved in acetic acid (225 ml) and treated with concentrated hydrochloric acid (75 ml). The resultin
35 solution was allowed to stir at RT for 14 h thereafter. At this time the reaction was concentrated, coevaporated

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with water (50 ml) and azeotropically dried by toluene
coevaporation (2 x 100 ml) to afford 7.8 g (96 % yield)
of the deprotected pentapeptide hydrochloride as a white
powder: ^{1}H NMR (D$_2$O) δ 1.29 - 1.39 (m, 12H), 1.47 (d, J
5 = 7.0 Hz, 3 H), 4.06 (q, J = 7.0 Hz, 1 H), 4.18 - 1.38
(m, 4 H); MS (LRFAB, NBA - HCl) 374 [M + H]$^+$.

H. Synthesis of Cyclo-(Ala-Ala-DAla-Ala-DAla-)

To a solution of Ala-Ala-DAla-Ala-DAla·HCl (7.8 g, 19.0
10 mmol) in DMF (2400 ml) at -40 °C was added DPPA (6.29 g,
22.8 mmol) and enough TEA to adjust the pH to ~8
(measured by spotting the reaction mixture on moistened
hydrion paper). This solution was allowed to stand at
-23 °C for 48 hours and at 8 °C for 48 hours. During
15 this time the pH was again maintained at ~8 with the
periodic addition of TEA. At the end of this period the
reaction mixture was poured into water (2400 ml) and
stirred with mixed-bed ion exchange resin (1200 g) for 6
h. The resin was removed by filtration and the filtrate
20 was concentrated to a volume of ~ 100 ml. Ether (500 ml)
was added and the precipitated white solid was isolated
by filtration and washed with more ether (250 ml). The
solid was then triturated by stirring with THF (100 ml)
for 12 h (to remove traces of DMF), filtered and
25 thoroughly dried to afford 3.15 g (47 % yield) of the
desired cyclic peptide as a fine white powder: ^{1}H NMR
(DMSO-d$_6$) δ 1.08 - 1.25 (m, 12 H), 1.24 (d, J = 7.3
Hz, 3 H), 4.00 - 4.10 (m, 1 H), 4.26 - 4.30 (m, 2 H),
4.34 (q, J = 7.2 Hz, 1 H), 4.41 (q, J = 7.6 Hz, 1 H),
30 7.58 (d, J = 7.0 Hz, 1 H), 7.83 (d, J = 8.4 Hz, 1 H),
8.22 (d, J = 6.2 Hz, 1 H), 8.33 (d, J = 7.81, 1 H), 8.49
(d, J = 6.8 Hz, 1 H); MS (HRFAB, NBA - HCl) m/z
356.1989 (M + H)$^+$; 356.1934 calcd for C$_{15}$H$_{25}$N$_5$O$_5$ (M + H)$^+$.

35

I.   Synthesis of (2S, 5R, 8S, 11R, 14S)-Pentamethyl-
1,4,7,10,13-pentaazacyclopentadecane
To a stirred suspension of *cyclo*-(Ala-Ala-DAla-Ala-DAla-
) (3.10 g, 8.70 mmol) in THF (70 ml) at RT was added

5   lithium aluminum hydride (108 ml of a 1.0 M solution in
THF, 108 mmol). The resulting mixture was stirred at RT
for 2 h and heated to reflux for 16 h thereafter. The
mixture was then cooled to --20 °C and quenched with the
dropwise addition of saturated sodium sulfate (~30 ml).

10 The resulting mixture was concentrated to a dry white
powder and this powder was triturated with ether (2 x
150 ml). The combined triturates were concentrated and
recrystallized form acetonitrile to afford 1.10 g (44 %
yield) of the desired ligand as a white solid: ^{1}H NMR

15 (CDCl$_3$) δ 0.96 (d, J = 5.2 Hz, 3 H), 1.00 (two
coincidental d, J = 5.0 Hz, 6 H), 1.02 (two coincidental
d, J = 5.0 Hz, 6 H), 1.30 - 1.55 (bm, 2 H), 1.85 - 2.15
(bs, 3 H), 2.05 - 2.19 (m, 5 H), 2.42 - 3.00 (complex
m, 12 H); MS (HRFAB, NBA - HCl) m/z = 286.3013 (M +

20 H)$^+$; 286.2971 calcd for C$_{15}$H$_{36}$N$_5$.

J.   Synthesis of [Manganese(II)dichloro-(2S, 5R, 8S,
11R, 14S)-Pentamethyl-1,4,7,10,13-
pentaazacyclopentadecane

25 To a stirred solution of anhydrous MnCl$_2$ (79.0 mg, 0.62
mmol) in hot ethanol (5 ml) was added (2S, 5R, 8S, 11R,
14S)-pentaazacyclopentadecane (177 mg, 0.62 mmol). The
solution was refluxed for 1 h and stirred at RT for an
additional 16 h. The solution was filtered through

30 celite, concentrated to half volume and treated with
ether (30 ml). The white crystals were isolated by
filtration and dried in vacuo to afford 187 mg (73 %
yield) of the complex as a white solid: MS (LRFAB, NBA)
m/z (relative intensity) = 410 (5) [M]$^+$, 375/377

35 (100/30) [M - Cl]$^+$; Anal. calcd. for C$_{15}$H$_{35}$N$_5$MnCl$_2$: C,

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43.75; H, 8.57; N, 17.01. Found: C,43.74; H, 8.60; N, 16.97.

Example 4

5   A. Synthesis of N-(p-toluenesulfonyl)-(R,R)-1,2-diaminocyclohexane

To a stirred solution of (R,R)-1,2-diaminocyclohexane (300 g, 2.63 mole) in CH_2Cl_2 (5.00 1) at -10° C was added a solution of p-

10   toluenesulfonylchloride (209 g, 1.10 mole) in CH_2Cl_2 (5.00 1) dropwise ofer a 7 h period, maintaining the temp at -5 to -10° C. The mixture was allowed to warm to room temp while stirring overnight. The mixture was concentrated in vacuo to a volume of 3 1 and the white

15   solid was removed by filtration. The solution was then washed with H_2O (10 x 1 1) and was dried over $MgSO_4$. Removal of the solvent in vacuo gave 286 g (97.5 % yield) of the product as a yellow crystalline solid: ^1H NMR ($CDCl_3$) δ 0.98 - 1.27 (m, 4 H), 1.54 - 1.66 (m, 2

20   H), 1.81 - 1.93 (m, 2 H), 2.34 (dt, J = 4.0, 10.7 Hz, 1 H), 2.42 (s, 3 H), 2.62 (dt, J = 4.2, 9.9 Hz, 1 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.77 (d, J = 8.3 Hz, 2 H); MS (LRFAB -   DTT - DTE) m/z 269 [M + H]$^+$.

25   B. Synthesis of N-(p-toluenesulfonyl)-N'-(Boc)-(R,R)-1,2-diaminocyclohexane

To a stirred solution of N-(p-toluenesulfonyl)-(R,R)-1,2-diaminocyclohexane prepared as in Example 1A (256 g, 0.955 mole) in THF (1.15 1) was added a 1 N

30   solution of aqueous NaOH (1.15 1, 1.15 mole). Di-t-butyldicarbonate (229 g, 1.05 mole) was then added and the resulting mixture was stirred overnight. The layers were separated and the aqueous layer was adjusted to pH 2 with 1 N HCl and saturated with NaCl. The aqueous

35   solution was then extracted with CH_2Cl_2 (2 x 500 ml) and the extracts and THF layer were combined and dried over

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MgSO₄. The solvent was removed in vacuo to give a
yellow solid. The crude product was purified by
crystallization from a THF-ether-hexanes mixture to give
310 g (88.1% yield) of the product as a white
5 crystalline solid: mp: 137 - 139° C; ^{1}H NMR (CDCl₃) δ
1.04 - 1.28 (m, 4 H), 1.44 (s, 9 H), 1.61 - 1.69 (m, 2
H), 1.94 - 2.01 (m, 2 H), 2.43 (s, 3 H), 2.86 (brs, 1
H), 3.30 (br d, J = 9.6 Hz, 1 H), 4.37 (br d, J = 6.7
Hz, 1 H), 5.48 (br d, J = 4.6 Hz, 1 H), 7.27 (d, J = 9.7
10 Hz, 2 H), 7.73 (d, J = 8.1 Hz, 2 H); MS (LRFAB, NBA -
Li) m/z 375 [M + Li]⁺.

C.   Synthesis of Boc-(R,R)-Cyc(Ts)-gly-OMe
To a stirred solution of N-(p-toluenesulfonyl)-N'-
15 (Boc)-(R,R)-1,2-diaminocyclohexane prepared as in
Example 1B (310 g, 0.841 mole) in anhydrous DMF (3.11 l)
at 0° C was added NaH (37.4 g - 60 % in oil, 0.934 mole)
in portions and the resulting mixture was stirred for 30
min. Methyl bromoacetate (142 g, 0.925 mole) was then
20 added dropwise over 45 min and the mixture was allowed
to warm to room temp while stirring overnight. After
stirring for 17 h, the solvent was removed in vacuo and
the residue was dissolved in ethyl acetate(3 l) and H₂O
(1 l). The ethyl acetate solution was washed with
25 saturated NaHCO₃ (1 l), saturated NaCl (500 ml) and was
dried over MgSO₄. The solvent was removed in vacuo and
the resulting oil was dissolved in ether.
Crystallization by the addition of hexanes gave 364 g
(98 % yield) of the product (TLC (98:2 CHCl₃-
30 MeOH/silica gel/UV detn) showed that the product
contained about 5% starting material) as colorless
needles: mp of pure sample 151 - 2° C ; ^{1}H NMR (CDCl₃) δ
1.11 - 1.22 (m, 4 H), 1.45 (s, 9 H), 1.64 - 1.70 (m, 3
H), 2.16 - 2.19 (m, 1 H), 2.43 (s, 3 H), 3.34 - 3.40 (m,
35 2 H), 3.68 (s, 3 H), 4.06 (ABq, J = 18.5 Hz, $\Delta \nu$ = 155
Hz, 2H), 4.77 (br s 1 H), 7.30 (d, J = 8.3 Hz, 2 H),

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7.82 (d, J = 8.3 Hz, 2 H); MS (LRFAB, DTT - DTE) m/z
441 [M + H]$^+$.

D. Synthesis of Boc-(R,R)-Cyc(Ts)-Gly-OH

5   To a stirred solution of impure Boc-(R,R)-Cyc(Ts)-
Gly-OMe prepared as in Example 1C (217 g, 0.492 mole) in
MeOH (1.05 l) was slowly added a 2.5N solution of
aqueous NaOH (295 ml, 0.737 mole) and the resulting
solution was stirred for 2 h. The solvent was removed
10 in vacuo and the residue was dissolved in H_2O (1.5 l).
The solution was filtered to remove a small amount of
solid andwas washed with ether (7 x 1 l) to remove the
impurity (compound 1B) which upon drying of the combined
washes over $MgSO_4$ and removal of the solvent in vacuo
15 resulted in recovery of 8.37 g. The pH of the aqueous
solution was then adjusted to 2 with 1 N HCl and the
product was extracted with ethyl acetate (3 x 1 l).
The extracts were combined, washed with saturated NaCl
(500 ml) and dried over $MgSO_4$. The solvent was removed
20 in vacuo and the residual ethyl acetate removed by
coevaporation with ether (500 ml) and then CH_2Cl_2 (500
ml) to give 205 g (97.6 % yield) of the product as a
white foam : ^{1}H NMR ($CDCl_3$) δ 1.15 - 1.22 (m, 4 H), 1.48
(s, 9 H), 1.55 - 1.68 (m, 3 H), 2.12 - 2.15 (m, 1 H),
25 2.43 (s, 3 H), 3.41 - 3.49 (m, 2 H), 3.97 (ABq, J = 17.9
Hz, $^\Delta\upsilon$ = 69.6 Hz, 2 H), 4.79 (br s, 1 H), 7.31 (d, J =
8.1 Hz, 2 H), 7.77 (d, J = 8.3 Hz, 2 H), 8.81 (br s, 1
H); MS (LRFAB, NBA - Li) m/z 433 [M + Li]$^+$.

30 E. Synthesis of N-(p-toluenesulfonyl)-(S,S)-1,2-
diaminocyclohexane
       To a stirred solution of (S,S)-1,2-
diaminocyclohexane (300 g, 2.63 mole) in CH_2Cl_2 (5.00 l)
at -10 C was added a solution of p-
35 toluenesulfonylchloride (209 g, 1.10 mole) in CH_2Cl_2
(5.00 l) dropwise over a 8 h period, maintaining the

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temp at -5 to -10°C. The mixture was allowed to warm to
RT while stirring overnight. The mixture was
concentrated in vacuo to a volume of 3 1 and the white
solid was removed by filtration. The solution was then
5 washed with H_2O (10 x 1 1) and was dried over $MgSO_4$.
Removal of the solvent in vacuo gave 289 g (98.3 %
yield) of the product as a yellow crystalline solid: ^1H
NMR ($CDCl_3$) δ 0.98 - 1.27 (m, 4 H), 1.55 - 1.66 (m, 2
H), 1.81 - 1.94 (m, 2 H), 2.32 (dt, J = 4.0, 10.9 Hz, 1
10 H), 2.42 (s, 3 H), 2.61 (dt, J = 4.0, 9.9 Hz, 1 H), 7.30
(d, J = 7.9 Hz, 2 H), 7.77 (d, J = 8.3 Hz, 2 H); MS
(LRFAB,GT - HCl) m/z 269 $[M + H]^+$.

15 F. Synthesis of N-(p-toluenesulfonyl)-N'-(Boc)-(S,S)-
1,2-diaminocyclohexane
      To a stirred solution of N-(p-toluenesulfonyl)-
(S,S)-1,2-diaminocyclohexane prepared as in Example 1E
(289 g, 1.08 mole) in THF (1.29 1) was added a 1 N
20 solution of aqueous NaOH (1.29 1, 1.29 mole). Di-t-
butyldicarbonate (258 g, 1.18 mole) was then added and
the resulting mixture was stirred overnight. The solid
was removed by filtration and washed with THF. The THF
layer was separated and the aqueous layer was adjusted
25 to pH 2 with 1 N HCl and saturated with NaCl. The
aqueous solution was then extracted with CH_2Cl_2 (2 x 500
ml) and the extracts and THF layer were combined, washed
with saturated NaCl (500 ml) and dried over $MgSO_4$. The
solvent was removed in vacuo to give a yellow slurry.
30 Crystallization with the addition of ether gave 364 g
(91.9 % yield) of the product as colorless needles: mp
137 - 139°C; ^1H NMR ($CDCl_3$) δ 1.06 - 1.31 (m, 4 H), 1.44
(s, 9 H), 1.60 - 1.69 (m, 2 H), 1.95 - 1.99 (m, 2 H),
2.42 (s, 3 H), 2.86 (br s, 1 H), 3.30 (br d, J = 2.6 Hz,
35 1 H), 4.41 (br d, J = 7.3 Hz, 1 H), 5.54 (br d, J = 5.4

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Hz, 1 H), 7.28 (d, J = 8.1 Hz, 2 H), 7.73 (d, J = 8.3
Hz, 2 H); MS (LRFAB, NBA - HCl) m/z 369 [M + H]+.

G. Synthesis of Boc-(S,S)-Cyc(Ts)-gly-OMe

5   To a stirred solution of N-(p-toluenesulfonyl)-N' -
(Boc)-(S,S)-1,2-diaminocyclohexane prepared as in
Example 1F (364 g, 0.989 mole) in anhydrous DMF (3.66 l)
at 0 C was added NaH (47.4 g - 60 % in oil, 1.19 mole)
in portions and the resulting mixture was stirred for
10 1.5 h. The mixture was warmed to room temp and stirred
an additional 30 min and then cooled back to 0 C.
Methyl bromoacetate (189 g, 1.24 mole) was added
dropwise over 30 min and the mixture was allowed to warm
to RT while stirring overnight. After stirring for 17
15 h, the solvent was removed in vacuo and the residue was
dissolved in a mixture of ethyl acetate(3 l) and H$_2$O (1
l). The layers were separated and the ethyl acetate
solution was washed with saturated NaHCO$_3$ (1 l), H$_2$O (1
l), saturated NaCl (2 x 500 ml) and was dried over
20 MgSO$_4$. The solvent was removed in vacuo and the
resulting oil was dissolved in ether. Crystallization
by the addition of hexanes gave 290 g of the crude
product as yellow needles. Another 180 g was recovered
from the filtrate as an oil. TLC (98:2 CHCl$_3$-
25 MeOH/silica gel/UV detn) showed that both the solid and
the oil contained starting material. ^{1}H NMR (CDCl$_3$) δ
1.06 - 1.29 (m, 4 H), 1.44 (s, 9 H), 1.58 - 1.66 (m, 3
H), 2.17 - 2.19 (m, 1 H), 2.43 (s, 3 H), 3.28 - 3.43 (m,
2 H), 3.68 (s, 3 H), 4.25 (ABq, J = 18.5 Hz, Δ ʋ = 115
30 Hz, 2H), 4.76 (br s 1 H), 7.31 (d, J = 8.3 Hz, 2 H),
7.83 (d, J = 8.3 Hz, 2 H); MS (LRFAB, NBA - Li) m/z 447
[M + H]+.

H. Synthesis of Boc-(S,S)-Cyc(Ts)-Gly-OH

35   To a stirred solution of impure Boc-(S,S)-Cyc(Ts)-
Gly-OMe prepared as in Example 1G (197 g, 0.447 mole) in

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MeOH (925 ml) was slowly added a 2.5N solution of
aqueous NaOH (268 ml, 0.670 mole) and the resulting
solution was stirred for 2 h. The solvent was removed
in vacuo and the residue was dissolved in H_2O (1 1).
5   The solution was washed with ether (4 x 1 1) to remove
the impurity (compound 1F) which upon drying of the
combined washes over $MgSO_4$ and removal of the solvent in
vacuo resulted in recovery of 14.8 g. The pH of the
aqueous solution was then adjusted to 2 with 1 N HCl and
10   the product was extracted with ethyl acetate (3 x 1 1).
The extracts were combined, washed with saturated NaCl
and dried over $MgSO_4$. The solvent was removed in vacuo
to give 171 g (89.7 % yield) of the product as an oil
which crystallized on standing: ^1H NMR ($CDCl_3$) δ 1.10 -
15   1.22 (m, 4 H), 1.45 (s, 9 H), 1.55 - 1.68 (m, 3 H), 2.13
- 2.16 (m, 1 H), 2.43 (s, 3 H), 3.39 - 3.41 (m, 2 H),
4.00 (ABq, J = 18.1 Hz, $\Delta \upsilon$ = 80.4 Hz, 2 H), 4.82 (br s,
1 H), 7.31 (d, J = 8.3 Hz, 2 H), 7.75 (d, J = 8.3 Hz, 2
H), 9.28 (br s, 1 H); MS (LRFAB, NBA - Li) m/z 433 [M +
20   Li]$^+$.

I.   Synthesis of   Boc-(S,S)-Cyc(Ts)-Gly-Gly-OEt
     To a stirred solution of Boc-(S,S)-Cyc(Ts)-Gly-OH
prepared as in Example 1H (26.7 g, 62.5 mmole) in
25   degassed anhydrous DMF (690 ml) was added HOBT (10.1 g,
75.0 mmole) and EDC-HCl (14.4 g, 75.0 mmole). After the
resulting solution was stirred for 30 min, glycine ethyl
ester hydrochloride (9.60 g, 68.8 mmole) was added and
the pH adjusted to 8 with TEA. After stirring for 2.75
30   days the solvent was removed in vacuo. The residue was
dissolved in a mixture of ethyl acetate (1 1) and H_2O (1
1) and the layers were separated. The aqueous layer was
extracted with ethyl acetate (1 1) and the extracts were
combine. The ethyl acetate solution was washed with 0.1
35   N HCl (1 1), saturated $NaHCO_3$ (1 1), saturated NaCl (500
ml) and was dried over $MgSO_4$. The solvent was removed

in vacuo to give 30.2 g (94.4 % yield) of the product as
a white foam: ^{1}H NMR (CDCl$_3$) δ 1.19 - 1.23 (m, 3 H), 1.28
(t, J =7.05 Hz, 3 H), 1.42 (s, 11 H), 1.63 - 1.71 (m, 2
H), 2.16 - 2.18 (m, 1 H), 2.43 (s, 3 H), 3.50 - 3.57 (m,
2 H), 3.83 (ABq, J = 17.7 Hz, delta v = 35.7 Hz, 2 H),
4.01 (dABq, J = 6.05, 17.92 Hz, Δ ^{v} = 28.9 Hz, 2 H),
4.20 (q, J = 7.3 Hz, 2 H), 4.88 (br s, 1 H), 7.31 (d, J
= 8.3 Hz, 2 H), 7.36 (br s, 1 H), 7.73 (d, J = 8.3 Hz, 2
H); MS (LRFAB, NBA - HCl) m/z 512 [M + H]$^+$.

J. Synthesis of (S,S)-Cyc(Ts)-Gly-Gly-OEt TFA salt
     To a stirred solution of Boc-(S,S)-Cyc(Ts)-Gly-Gly-
OEt prepared as in Example 1I (30.1 g, 58.8 mmole) in
CH$_2$Cl$_2$ (265 ml) was added TFA (63 ml) and the resulting
solution was stirred for 30 minutes. The solvent was
removed in vacuo and residual TFA was coevaporated with
CH$_2$Cl$_2$ (2 x 1 l) and ether (1 l). The oil was then
triturated with ether (2 x 1 l) and the ether decanted.
The resulting foam was dried in vacuo to give 33.7 g
(assumed quantitative yield) of the product as a tan
powder: ^{1}H NMR (CDCl$_3$) δ 0.96 - 1.23 (m, 4 H), 1.25 (t, J
= 7.3 Hz, 3 H), 1.51 - 1.66 (m, 3 H), 2.12 - 2.26 (m, 1
H), 2.41 (s, 3 H), 2.98 - 3.10 (brs, 1 H), 3.67 - 3.71
(m, 1 H), 4.04 (ABq, J = 17.7 Hz, Δ ^{v} = 154 Hz, 2 H),
4.04 (d, J = 4.4 Hz, 2 H), 4.17 (q, J = 7.3 Hz, 2 H),
7.29 (d, J = 8.3 Hz, 2 H), 7.70 (d, J = 8.3 Hz, 2 H),
8.04 (br s, 1 H), 8.14 (br s, 3 H) MS (LRFAB, NBA - HCl)
m/z 412 [M + H]$^+$.

K. Synthesis of Boc-(R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-
Gly-Gly-OEt
     To a stirred solution of Boc-(R,R)-Cyc(Ts)-Gly-OH
prepared as in Example 1D (25.1 g, 58.8 mmole) in
degassed anhydrous DMF (650 ml) was added HOBT (9.54 g,
70.6 mmole) and EDC-HCl (13.5 g, 70.6 mmole). After the
resulting solution was stirred for 30 min (S,S)-Cyc(Ts)-

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Gly-Gly-OEt TFA salt prepared as in Example 1J (33.6 g, 58.8 mmole) was added and the pH was adjusted to 8 with TEA. After stirring for 2.75 days, the solvent was removed in vacuo. The residue was dissolved in a
5 mixture of ethyl acetate (1 1) and H_2O (1 1) and the layers were separated. The ethyl acetate solution was washed with 0.1 N HCl (2 x 1 1), saturated $NaHCO_3$ (2 x 1 1), saturated NaCl (500 ml) and was dried over $MgSO_4$. The solvent was removed in vacuo to give 47.5 g (98.4 %
10 yield) of the product as a tan foam: ^1H NMR ($CDCl_3$) δ 1.12 - 1.83 (m, 26 H), 2.21 - 2.24 (m, 2 H), 2.42 (s, 3 H), 2.43 (s, 3 H), 3.36 - 3.51 (br s, 2 H), 3.68 -3.96 (m, 6 H), 4.00 (d, J = 5.4 Hz, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.72 (br s, 1 H), 6.78 (br s, 1 H), 7.31 (d, J
15 = 8.1 Hz, 4 H), 7.46 (br s, 1 H), 7.79 (m, 4 H); MS (LRFAB, NBA - HCl) m/z 820 [M + H]⁺.

L.   Synthesis of   Boc-(R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-Gly-Gly-OH

20   To a stirred solution of Boc-(R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-Gly-Gly-OEt prepared as in Example 1K (47.4 g, 57.8 mmole) in MeOH (240 ml) was added a 2.5 N solution of aqueous NaOH (34.7 ml, 86.7 mmole) and the resulting solution was stirred for 2 h. The solvent was
25 removed in vacuo and the residue was dissolved in H_2O (1 1). The aqueous solution was washed with ether (2 x 1 1) and the pH was adjusted to 2 with 1 N HCl. The solution was then saturated with NaCl and extracted with ethyl acetate (3 x 1 1). The combined extracts were
30 dried over $MgSO_4$ and the solvent was removed in vacuo. The residual ethyl acetate was removed by coevaporation with CH_2Cl_2 and the resulting foam was dried in vacuo to give 45.7 g (99.7 % yield) of the product as a tan powder: ^1H NMR ($CDCl_3$) δ 1.16 - 1.75 (m, 23 H), 2.13 -
35 2.17 (m, 2 H), 2.41 (s, 3 H), 2.42 (s, 3 H), 3.49 - 4.16 (m, 10 H), 4.53 (br s, 1 H), 7.01 (br s, 1 H), 7.30 (d,

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J = 8.1 Hz, 4 H), 7.40 (br s, 1 H), 7.79 (d, J = 8.1 Hz,
2 H), 7.86 (d, J = 7.7 Hz, 2 H), 10.40 (br s, 1 H); MS
(LRFAB, NBA - HCl) m/z 792 [M + H]⁺.

5 M.   Synthesis of   (R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-Gly-
   Gly-OH TFA salt
        To a stirred solution of Boc-(R,R)-Cyc(Ts)-Gly-
   (S,S)-Cyc(Ts)-Gly-Gly-OH prepared as in Example 1L (45.5
   g, 57.5 mmole) in CH₂Cl₂ (260 ml) was added TFA (60 ml).
10 The resulting solution was stirred for 30 min and the
   solvent was removed in vacuo. Residual TFA was removed
   by coevaporation with CH₂Cl₂ (3 x 1 l) and trituration of
   the resulting foam with ether (1 l, 2 x 750 ml),
   decanting the ether each time. After dessication in
15 vacuo, 47.4 g (100 % yield) of the product was was
   obtained as an off white powder: ¹H NMR (CDCl₃) δ 1.05 -
   1.31 (m, 9 H), 1.48 - 1.63 (m, 5H), 2.11 - 2.21 (m, 2
   H), 2.40 (s, 3 H), 2.42 (s, 3 H), 3.25 (br s, 1 H), 3.60
   - 3.80 (m, 3 H), 3.83 - 4.19 (m, 6 H), 6.94 (br s, 1 H),
20 7.31 (m, 4 H), 7.69 (m, 4 H), 7.83 (br s, 3 H), 13.17
   (br s, 2 H); MS (LRFAB, DTT - DTE) m/z 692 [M + H]⁺.

   N.   Synthesis of Cyclo-[(R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-
   Gly-Gly-]
25   To a stirred solution of (R,R)-Cyc(Ts)-Gly-(S,S)-
   Cyc(Ts)-Gly-Gly-OH TFA salt prepared as in Example 1M
   (32.2 g, 40.0 mmole) in degassed anhydrous DMF (10.0 l)
   at -78 C was added DPPA (13 4 g, 48.8 mmole). The pH
   of the solution was then adjusted to 8 with TEA and the
30 solution was allowed to stand for 6 h at -78 C. The pH
   was readjusted to 8 with TEA and the solution was warmed
   to -45 C for 24 h. After readjusting the pH as
   before, the solution was allowed to warm to -40 C for
   24 h. The pH was adjusted as before and the solution was
35 allowed to stand at -20 C for 24 h. The pH was
   readjusted as before and the solution was allowed to

warm to 2° C over 24 h. The pH had dropped only
slightly. The pH was readjusted as before and the
solution was allowed to stand at 2° C for another 24 h
after which time the pH had not changed. The solution
5   was divided equally among 6 - 4 1 beakers and H₂O (1.1 1)
was addedto each. Then added a total of 5.00 kg mixed-
bed ion exchange resin to the solution (divided equally
among the 6 beakers) and stirred the mixtures for 6 h.
The resin was then filtered and washed with DMF. The
10 solvent was then removed in vacuo and the solid residue
was dissolved in MeOH (100 ml) and filtered to remove
finely divided solids. The solution was then
concentrated in vacuo to a volume of 25 ml and ether was
added periodically as the crystallization proceeded to
15 give 22.2 g (82.5 % yield) of the product as colorless
needles; mp 190 - 200° C; ¹H NMR (CDCl₃) δ 0.87 - 2.13
(m, 16 H), 2.41 (s, 3 H), 2.45 (s, 3 H), 3.56 - 3.97 (m,
10 H), 6.66 (br s, 1 H), 7.18 (br s, 1 H), 7.34 (d, J =
8.1 Hz, 4 H), 7.65 (br s, 1 H), 7.71 (d, J = 7.3 Hz, 2
20 H), 7.89 (d, J = 7.3 Hz, 2 H); MS (LRFAB, NBA - Li) m/z
680 [M + Li]⁺.

O.   Synthesis of 2,3-(R,R)-8,9-(S,S)-Bis-cyclohexano-
1,4,7,10,13-pentaazacyclopentadecane
25   To a stirred solution of Cyclo-[(R,R)-Cyc(Ts)-Gly-
(S,S)-Cyc(Ts)-Gly-Gly] prepared as in Example 1N (19.4
g, 28.8 mmole) in anhydrous THF (475 ml) was added a
solution of 1.0 M LiAlH₄ in THF (345 ml, 345 mmole)
dropwise over 30 min. The yellow homogeneous solution
30 was refluxed for 20 h (by which time it had become
heterogeneous) and was then cooled to 0° C. The mixture
was then quenched by the dropwise addition of a 10 %
NaSO₄ solution (50 ml) while cooling in an ice bath. The
solids were removed by filtration under an Ar blanket
35 and the THF was removed in vacuo to give an oil which
rapidly crystallized. The solids were then refluxed

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with anhydrous THF (1 l) for 1 h and the mixture was
filtered and the solvent removed in vacuo as before.
The solids were then refluxed with a mixture of THF (1
l) and MeOH (500 ml) for 1 h and worked up as before.

5   The residues from the extractions were then dissolved in
anhydrous THF, combined and solids were removed by
filtration. The solvent was removed in vacuo and the
yellow foam dried by azeotroping H_2O with toluene (1.75
l) in vacuo at 90° C. Then refluxed the solids with

10   hexanes (1 l) for 30 min and transferred the hot
solution to a tared flask and removed the solvent in
vacuo to give 6.1 g of an oil which crystallized on
standing. The remaining solids were refluxed with
hexanes as before and obtained 1.4 g of an oil which

15   crystallized on standing. The solids were then
dissolved in MeOH and toluene (1 l) was added. The
solvent was removed in vacuo and any remaining H_2O was
removed by azeotroping with toluene (1 l) and then
hexanes (3 x 1 l). The resulting fine powder was

20   refluxed with hexanes (1 l) for 2 h under argon and
filtered into a tared flask. The solvent was removed in
vacuo to give 1.7 g oil which crystallized on standing.
The crystalline residues from the 3 extracts were
dissolved in hexanes and combined. A small amount of

25   haziness was removed by filtration and the solution was
concentrated to give 5.3 g (57 % yield) of product as a
pale yellow crystalline solid. Recrystallization from
acetonitrile gave 4.47 g (48.0 % yield) of a colorless
crystalline solid: mp 107 - 8° C; ^1H NMR ($CDCl_3$) δ 0.95 -

30   1.01 (m, 4 H), 1.19 - 1.24 (m, 4 H), 1.70 - 1.73 (m, 4
H), 1.97 (br s, 5 H), 2.08 - 2.14 (m, 8 H), 2.49 - 2.68
(m, 6 H), 2.74 - 2.80 (m, 2 H), 2.85 - 2.90 (m, 2 H),
2.94 - 2.99 (m, 2 H); MS (LRFAB, NBA) m/z 324 [M + H]$^+$;
Anal. calcd. for $C_{18}H_{37}N_5$: C, 66.83; H, 11.53; N, 21.65.

35   Found: C, 66.80; H, 11.44; N, 21.71.

P.   Synthesis of [Manganese(II) dichloro (2,3-(R,R)-8,9-(S,S)-Bis-cyclohexano-1,4,7,10,13-pentaazacyclopentadecane] chloride

To a stirred solution of anhydrous $MnCl_2$ (1.67 g,
5   13.3 mmole) in hot methanol (120 ml) was added 2,3-
(R,R)-8,9-(S,S)-bis-cyclohexano-1,4,7,10,13-
pentaazacyclopentadecane prepared as in Example 10 (4.30
g, 13.3 mmole) and the solution was refluxed and then
stirred at room temp overnight. Crystallization from
10 ether gave 5.11 g (85.6 % yield) of the product as an
off-white crystalline solid: MS (LRFAB, NBA) m/z
(relative intensity) 448 (2) $[M]^+$, 413/415 (100,33) [M -
$Cl]^+$; Anal. calcd. for $C_{18}H_{37}N_5MnCl_2$: C, 48.11; H, 8.30; N,
15.59; Cl, 15.78. Found: C, 48.18; H, 8.32; N, 15.56;
15 Cl, 15.75.

Example 5

A.   Synthesis of Boc-DSer(OBzl)-OMe

To Boc-DSer(OBzl)-OH (15.0 g, 50.8 mmol) win ACN (250
20 ml) was added Cs2CO3 (33.0 g, 102 mmol) and methyl
iodide (6.32 ml, 102 mmol) and the resulting mixture was
stirred at RT for 3 h thereafter. At this time the
reaction was filtered and concentrated. The residue was
partitioned between water (250 ml) and ethyl acetate
25 (250 ml). The ethyl acetate layer was dried (MgSO4),
filtered and concentrated to afford 15.0 g (95 % yield)
of the desired methyl ester as a white solid: ^1H NMR
(DMSO-d_6) δ 1.40 (s, 9 H), 3.64 (s, 3 H), 3.58 - 3.73
(m, 2 H), 4.32 (bq, J = 6.2 Hz, 1 H), 4.49 (s, 2 H),
30 7.16 (bd, J = 6.2 Hz, 1 H), 7.25 - 7.38 (m, 5 H); MS
(HRFAB, NBA - Li) m/z = 316.1768 $[M + Li]^+$; 316.1736
calcd for $C_{16}H_{23}O_5NLi$.

B.   Synthesis of DSer(OBzl)-OMe•TFA

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Boc-DSer(OBzl)-OMe (15.0 g, 48.6 mmol) was dissolved in
methylene chloride (125 ml) and treated with TFA (32
ml). The resulting mixture was stirred at RT for 30 min
and concentrated. The oil was triturated with ether
5 (400 ml) to remove residual TFA to afford 15.9 g (>100
%yield, contains a small amount of residual TFA) of the
desired TFA salt as a colorless oil: ^{1}H NMR (DMSO-d_6) δ
3.72 (s, 3 H), 3.73 - 3.83 (m, 2 H), 4.36 (bt, J = 3.3
Hz, 1 H), 5.50 (ABq, J = 12 Hz, Δ^v = 24 Hz , 2 H), 7.27 -
10 7.37 (m, 5 H), 8.72 (bs, 3 H); MS (HRFAB, NBA - HCl)
210.1159 [M + H]$^+$; 210.1130 calcd for $C_{11}H_{16}NO_3$.

C. Synthesis of Boc-Ser(OBzl)-DSer(OBzl)-OMe
Boc-Ser(OBzl)-OH (14.5 g, 49.2 mmol) was dissolved in
15 DMF (550 ml) and treated with HOBT•H_2O (9.03 g, 59.0
mmol) followed by EDC•HCl (11.3 g, 59.0 mmol). The
resulting solution was stirred for 20 min at RT and
treated with DSer(OBzl)-OMe•TFA (15.9 g, 49.2 mmol) and
TEA (8.22 ml, 59 mmol) and this solution was allowed to
20 stir for 12 h thereafter. The DMF was evaporated and
the residue was taken up into ethyl acetate (300 ml).
The ethyl acetate solution was washed with 1 N sodium
bisulfate (100 ml), water (100 ml), saturated sodium
bicarbonate (100 ml), brine (100 ml) and dried (MgSO$_4$).
25 Filtration and concentration afforded 20.8 g (87 %
yield) of the desired dipeptide as a white solid: ^{1}H NMR
(DMSO-d_6) δ 1.37 (s, 9H), 3.57 - 3.75 (m, 4 H), 3.62
(s, 3 H), 4.35 - 4.50 (m, 1 H), 4.46 (s, 3 H), 4.57 -
4.63 (m, 1 H), 6.88 (d, J = 8.1 Hz, 1 H), 7.20 - 7.34
30 (m, 10 H), 8.34 (d, J = 8.1 Hz, 1 H); MS (HRFAB, NBA -
Li) m/z = 493.2559 [M + Li]$^+$; 493.2526 calcd for
$C_{26}H_{34}N_2O_7Li$.

35 D. Synthesis of Ser(OBzl)-DSer(OBzl)-OMe•TFA

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Boc-Ser(OBzl)-D-Ser(OBzl)-OMe (20.4 g, 42.0 mmol) was
dissolved int methylene chloride (170 ml) and TFA (43
ml) was added. The resulting mixture was stirred at RT
for 30 min and concentrated. The residue was triturated
5   with ether (400 ml) to remove excess TFA to afford 22.7
g (>100 %, contains excess TFA) of the desired TFA salt:
^{1}H NMR (DMSO-d_6) δ 3.59 - 3.64 (m, 1 H), 3.67 (s, 3 H),
3.70 - 3.85 (m, 3 H), 4.23 (bs, 1 H), 4.40 - 4.58 (m, 4
H), 4.60 - 4.70 (m, 1 H), 7.20 - 7.39 (m, 10 H), 8.41
10 (bs, 3 H), 9.09 (d, J = 7.81 Hz, 1 H); MS (HRFAB, NBA -
HCl) m/z = 387.1927 [M + H]$^+$; 387.1920 calcd for
$C_{21}H_{27}N_2O_5$.

E.   Synthesis of Boc-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe
15 To a solution of Boc-DSer(OBzl)-OH in DMF (480 ml) was
added HOBT•H_2O (7.96 g, 52.0 mmol) followed by EDC•HCl
(9.97 g, 52.0 mmol) and the resulting solution was
stirred for 20 min at RT. To this solution was added
Ser(OBzl)-DSer(OBzl)-OMe•TFA (21.7 g, 43.3 mmol) and TEA
20 (7.25 ml, 52.0 mmol) and the resulting mixture was
stirred for 16 h thereafter. The DMF was evaporated and
the residue was partitioned between water (100 ml) and
ethyl acetate (300 ml). The ethyl acetate solution was
washed with 1 N sodium bisulfate (150 ml), water (150
25 ml), saturated sodium bicarbonate (150 ml) and brine
(150 ml), dried (Na_2SO_4), filtered and concentrated to
afford 26.6 g (93 % yield) of the desired tripeptide as
a white foam: ^{1}H NMR (DMSO-d_6) δ 1.39 (s, 9 H), 3.56 -
3.74 (complex m, 6 H), 3.64 (s, 3 H), 4.35 - 4.43 (m, 1
30 H), 4.43 -4.50 (m, 6 H), 4.63 (m, 1 H), 4.73 (m, 1 H),
6.94 (d, J = 7.8 Hz, 1 H), 7.24 - 7.36 (m, 15 H), 8.13
(d, J = 8.2 Hz, 1 H), 8.51 (d, J = 7.8 Hz, 1 H); MS
(HRFAB, NBA - Li) m/z = 670.3326 [M + Li]$^+$; 670.3316
calcd for $C_{36}H_{45}N_3O_9Li$.

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F. Synthesis of DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe•TFA
salt

To a solution of Boc-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe
(26.4 g, 39.7 mmol) in methylene chloride (220 ml) was
5   added TFA (55 ml) and the resulting solution was stirred
at RT for 30 min and concentrated. The residue was
triturated with ether (300 ml) and the ether triturate
was decanted and dicarded affording 26.2 g (97 % yield)
of the TFA salt as an orange oil after vacuum drying;
10 ^{1}H NMR (DMSO-d_6) δ 3.55 - 3.3.83 (complex m, 6 H), 3.65
(s, 3 H), 4.21 (bs, 1 H), 4.40 - 4.58 (m, 6 H), 4.60 -
4.67 (m, 1 H), 4.85 -4.94 (m, 1 H), 7.20 - 7.40 (m, 15
H), 8.37 (bs, 3 H), 8.78 (d, J = 7.8 Hz, 1 H), 8.84 (d,
J = 8.3 Hz, 1 H);   MS (HRFAB, NBA - Li) m/z = 570.2790
15 [M + Li]$^{+}$; 570.2792 calcd for $C_{31}H_{37}N_3O_7Li$.

G. Synthesis of Boc-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-D-
Ser(OBzl)-OMe

To a solution of Boc-Ser(OBzl)-OH (11.2 g, 38.0 mmol)
20 was added HOBT•H2O (6.99 g, 45.6 mmol) and EDC•HCl (8.74
g, 45.6 mmol) and the resulting mixture was stirred at
RT for 30 min. At this time DSer(OBzl)-Ser(OBzl)-
DSer(OBzl)-OMe (25.8 g, 38.0 mmol) was added followed by
TEA (6.36 ml, 45.6 mmol). The resulting solution was
25 allowed to stir for 16 h thereafter. The DMF was
evaporated and the residue was partitioned between water
(200 ml) and ethyl acetate (400 ml). The ethyl acetate
solution was washed with 1 N sodium bisulfate (200 ml),
water (200 ml), saturated sodium bicarbonate (200 ml),
30 and brine (200 ml), dried (MgSO$_4$), filtered and
concentrated to afford 30.2 g (95 % yield) of the
desired tetrapeptide as a white foam; ^{1}H NMR (DMSO-d_6)
δ 1.38 (s, 9 H), 3.53 - 3.76 (complex m, 8 H), 3.64 (s,
3 H), 4.34 - 4.42 (m, 1 H), 4.40 - 4.51 (m, 8 H), 4.58 -
35 4.66 (m, 1 H), 4.67 - 4.77 (m, 1 H), 4.74 - 4.82
(apparent q, J = 7.8 Hz, 1 H), 6.89 (d, J = 8.2 Hz, 1

H), 7.22 - 7.38 (m, 20 H), 8.14 (d, $J = 7.6$ Hz, 1 H),
8.34 (d, $J = 7.8$ Hz, 1 H), 8.55 (d, $J = 7.8$ Hz, 1 H);
MS (HRFAB, NBA - Li) m/z = 847.4095 [M + Li]*; 847.4106
calcd for $C_{46}H_{56}N_4O_{11}Li$.

H. Synthesis of Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe•TFA

Boc-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe (30.2
g, 35.9 mmol) was dissolved in methylene chloride (250
ml) and treated with TFA (63 ml). The resulting mixture
was stirred for 30 min at RT and concentrated.
Trituration with ether afforded 30.0 g (98 % yield) of
the desired TFA salt as the oily residue; ^{1}H NMR (DMSO-
d_6) δ 3.50 - 3.85 (complex m, 8 H), 3.65 (s, 3 H), 4.21
(bs, 1 H), 4.40 - 4.55 (m, 8 H), 4.58 - 4.66 (m, 1 H),
4.80 - 4.95 (m, 2 H), 7.20 - 7.40 (m, 20 H), 8.35 (bs, 3
H), 8.54 (d, $J = 8.2$ Hz, 1 H), 8.69 (d, $J = 7.4$ Hz, 1
H), 8.86 (d, $J = 8.2$ Hz, 1 H); MS (HRFAB, NBA - Li) m/z
= 747.3590 [M + Li]*; 747.3581 calcd for $C_{41}H_{48}N_4O_9Li$.

I. Synthesis of Boc-Ser(OBzl)-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe

To a solution of Boc-Ser(OBzl)-OH (10.1 g, 34.2 mmol) in
DMF (380 ml) was added HOBT•H$_2$O (6.28 g, 41.0 mmol)
followed by EDC•HCl (7.86 g, 41.0 mmol) and the
resulting mixture was stirred for 20 min at RT.
Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe•TFA (29.2
g, 34.2 mmol) was added followed by the addition of TEA
(5.71 ml, 41.0 mmol) and the reaction was allowed to
stir for 12 h thereafter. The DMF was evaporated and
the residue was partitioned between water (200 ml) and
ethyl acetate (400 ml). The ethyl acetate layer was
washed with 1 N sodium bisulfate (200 ml), water (200
ml), saturated sodium bicarbonate (200 ml) and brine
(200 ml), dried (MgSO$_4$), filtered and concentrated to

afford 33.7 g (97 % yield) of the desired pentapeptide
as a white powder; ^{1}H NMR (DMSO-d$_6$) δ 1.39 (s, 9 H),
3.55 - 3.77 (complex m, 10 H), 3.64 (s, 3 H), 4.32 -
4.42 (m, 1 H), 4.40 - 4.54 (m, 10 H), 4.60 - 4.68 (m, 1
5   H), 4.49 - 4.84 (m, 3 H), 7.00 (d, J = 7.7 Hz, 1 H),
7.20 - 7.40 (m, 25 H), 8.11 (d, J = 7.4 Hz, 1 H), 8.30
(d, J = 7.8 Hz, 1 H), 8.35 (d, J = 7.8 Hz, 1 H), 8.58
(d, J = 7.8 Hz, 1 H); MS (LRFAB, NBA - Li) m/z = 1024
[M + Li]$^+$.

10

J.   Synthesis Ser(OBzl)-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-
DSer(OBzl)•HCl
Boc-Ser(OBzl)-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-
OMe (31.7 g, 31.1 mmol) was dissolved in acetic acid
15 (760 ml) and treated with concentrated HCl (190 ml).
The resulting solution was stirred at RT for 12 h
thereafter. Concentration afforded 29.3 g (100 %) of
the desired deprotected peptide salt as a white foam; ^{1}H
NMR (DMSO-d$_6$) δ 3.55 - 3.90 (complex m, 10 H), 4.20 (m,
20 1 H), 4.38 - 4.61 (m, 11 H), 4.73 - 4.85 (m, 3 H), 7.20 -
7.40 (m, 25 H), 8.34 - 8.42 (m, 2 H), 8.49 (m, 4 H),
8.95 (d, J = 7.7 Hz, 1 H); (LRFAB, NBA - HCl] m/z = 905
[M + H]$^+$.

25 K.   Synthesis of Cyclo-[Ser(OBzl)-Ser(OBzl)-DSer(OBzl)-
Ser(OBzl)-DSer(OBzl)-]
A solution of Ser(OBzl)-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-
DSer(OBzl)•HCl (29.4 g, 31.3 mmol) in anhydrous degassed
DMF (4000 ml) was cooled to -40 °C and treated with DPPA
30 (8.22 ml, 38.1 mmol) followed by TEA (4.53 ml, 32.5
mmol). The reaction was stored at -20 °C for 48 h and
at 0 °C for 48 h thereafter. During this time the "pH"
was maintained at ~8 by periodic addition of TEA
(measured by spotting reaction mixture on moistened
35 Hydrion paper). After this reaction period the reaction
was diluted with water (1000 ml) and stirred with mixed

bed ion-exchange resin (1600 g) for 6 h. The resin was
removed by filtration and the filtrate was concentrated
to a volume of ~200 ml. The product was precipitated by
the addition of water (500 ml). The solid was filtered
5   and washed with ether (250 ml) to afford after vacuum
desiccation 20.5 g (74 % yield) of the desired cyclic
peptide as a white powder: ^{1}H NMR (DMSO-d_6, *major
conformer*) δ 3.50 - 3.83 (complex m, 11 H), 4.32 - 4.82
(complex m, 14 H), 7.18 - 7.38 (m, 25 H), 7.56 (d, J =
10 6.8 Hz, 1 H), 7.94 (d, J = 8.7 Hz, 1 H), 8.50 (d, J =
6.0 Hz, 1 H), 8.78 (m, 2 H); ; (LRFAB, NBA - Li] m/z =
893 [M + Li]$^+$.

L. Synthesis of (2S, 5R, 8S, 11R, 14S)-
15 Penta(benzyloxymethyl)-1,4, 7, 10, 13-pentaazacyclo-
pentadecane.
To a solution of the *Cyclo*-[Ser(OBzl)-Ser(OBzl)-
DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-] (7.00 g, 7.90 mmol) in
THF (100 ml) was added lithium aluminum hydride (100 ml
20 of a 1.0 M solution in THF, 100 mmol) over 5 min at RT.
The resulting solution was heated at reflux for 16 h
thereafter. The mixture was cooled to ~-20 °C and
quenched (cautiously) with 5% sodium sulfate solution
(30 ml). The resulting mixture was concetrated to a
25 white powder and this powder was thoroughly dried by
coevaporation with toluene (3 x 50 ml). The residue
was triturated with ether (2 x 100 ml) and the combined
triturates were concentrated to afford 6.1 g (95 %
yield) of the desired ligand as a yellow oil; ^{1}H NMR
30 (CDCl$_3$) δ 1.95 (bs, 5 H), 2.30 - 3.60 (complex m, 25
H), 4.20 - 4.40 (m, 10 H), 7.00 - 7.38 (m, 25 H); MS
(HRFAB, NBA - Li) m/z = 822.5174 [M + Li]$^+$; 822.5146
calcd for $C_{50}H_{65}N_5O_5Li$.

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M.   Synthesis of [Manganese(II)dichloro(2S, 5R, 8S, 11R,
14S)-penta(hydroxymethyl)-1,4,7, 10,13-
pentaazacyclopentadecane.

To a solution fo manganese(II) chloride (221 mg, 1.76

5   mmol) in methanol (75 ml) was added (2S, 5R, 8S, 11R,
14S)-penta(benzyloxymethyl)-1,4,7,10,13-
pentaazacyclopentadecane (1.43 g, 1.75 mmol) and the
reaction mixture was refluxed for 2 h and stirred at RT
for 12 h thereafter. The methanol solution was

10 evaporated and the residual oil was redissolved in
ethanol (10 ml) and water (1 ml) in a Parr bottle. This
mixture was treated with 10 % Pd on carbon (1 g) and
hydrogenolyzed at 60 C and 65 psi for 16 h thereafter.
Filtration, concentration and recyrstallization from

15 ethanol-ether afforded 212 mg (29 % yield) of the
desired complex as a white solid;   MS (HRFAB, NBA) m/z
= 455.1718 [M - Cl]$^+$; 455.1707 calcd for $C_{15}H_{35}N_5MnCl$.

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Example 6

Relaxivity measurements of the complexes of the invention (Examples 2-5) and of a comparative complex
5 (Example 1) were determined and the results are found in Table I.

Proton relaxation times (T_1) of the sample in 100mM Hepes buffer, pH=7.4, at 40°C were determined from a monoexponential curve fit obtained from inversion-
10 recovery pulse sequences (180°-τ-90°) with a Bruker PC 120/125/10 VTs NMR process analyzer. The spectrometer was calibrated for each sample to assure accurate duration of 90° and 180° radio frequency pulses and appropriate magnetic field strength to match the 20 MHz
15 system operating frequency. The relaxivity (R_1) was obtained from the slope of a plot of $1/T_1$ versus the concentration of paramagnetic compound.

The relaxation time (T_2) of each sample in 100 mM Hepes buffer, pH=7.4, was measured at 40°C using a Carr-
20 Purcel-Meiboom-Gill pulse sequence on the same Bruker instrument. The relaxivity (R_2) was obtained from a plot of $1/T_2$ versus the concentration of the paramagnetic compound.

25   Table I

Sample	Relaxivity, $mM^{-1}sec^{-1}$	
	R_1	R_2
Example 1 (Comparative)	1.82	2.37
30 Example 2	2.09	2.49
Example 3	2.76	3.86
Example 4	2.10	2.61
Example 5	3.48	5.93

35

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        The results found in Table I demonstrate that the
    complexes of the invention (Examples 2-5) have improved
    relaxivities compared to the comparative complex
    (Example 1).

5

                            Example 7

        Kinetic stability measurements of the complexes of
    the invention (Examples 2-4) and of the comparative
10 complex (Example 1) were determined and the results are
    found in Table II.
        The kinetic stability constant (k_{diss}) for each
    complex can be determined by observing the rate at which
    copper appears to replace manganese as the metal center
15 of the manganese macrocyclic complexes at different
    pH's.
        A Beckman model DU-70 UV/VIS spectrometer was set
    up to scan the wavelengths from 700 to 200 nanometers.
    Concentrations of the complexes were kept low enough to
20 stay within the linear range of observable absorbents
    for the DU-70, which is below 2.00 absorbents units.
        Since copper has an observable absorbency band
    within the experimental range of wavelengths and binding
    energies that are much higher than that of manganese,
25 the replacement of copper for manganese as the metal
    center is almost instantaneous. Therefore, copper is a
    good choice as a tracer of the decomposition of
    manganese from the macrocyclic ligand system.

30

35

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Table II

Example No.	Kinetic Stability, k_{diss} ($M^{-1}Sec^{-1}$)
1 (Comparative)	2814
2	1375
3	17.7
4	31.5
5	ND^1

[1] Not Determined

The data in Table II demonstrates that the
complexes of the invention (Examples 2-4) are
substantially more kinetically stable than the
comparative complex (Example 1).

Example 8

Oxidation potentials of the complexes of the
invention (Examples 2-4) and of the comparative complex
(Example 1) were determined and the results are found in
Table III.

Cyclic voltammograms were run in methanol
containing 0.18M tetrabutylammonium chloride under
nitrogen using a glassy carbon electrode with a platinum
reference electrode and ferrocene internal standard.

Table III

Example No.	Oxidation Potential, $E_{1/2}$ (volts)
1 (Comparative)	0.70
2	0.75
3	0.85
4	0.74
5	ND^1

[1] Not Determined

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The results in Table III demonstrates that the
manganese(II) complexes of the invention (Examples 2-4)
are more oxidatively stable than the comparative
manganese(II) complex (Example 1).

5

Example 9

The partition coefficient (log P) of the complexes
of the invention (Examples 2-5) and of a comparative
10   complex of (Example 1) were determined and the results
are found in Table IV.

The partition coefficient was determined by
measuring the manganese contents in each of the buffer
and octanol phases. About 5mg of sample was dissolved
15   in a 5mL octanol saturated buffer solution (10 mM
Hepes/150mM NaCl, pH=7.4). The sample solution was
mixed with 5mL of buffer saturated octanol and shaken
overnight. The mixed solution was centrifuged to
separate the two phases. 2mL of solution (in duplicate)
20   was taken from each phase and digested with an acid
mixture. The prepared solutions were then measured for
manganese using ICP-AES and/or ICP-MS. The log P value
was calculated from the Mn(octanol)/Mn(buffer) ratio.

25   Table IV

Example No.	Partition Coefficient, log P
1 (Comparative)	-2.9
2	-1.9
3	-1.1
4	-0.76
5	-3.2

35   The results in Table IV demonstrate that the log P,
i.e. lipophilicity or biodistribution, of the complexes

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of the invention (Examples 2-5) can be controlled by
controlling the substitutents on the macrocycle.

5

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CLAIMS

That which is claimed is:

1.   A method of magnetic resonance imaging
comprising:

5   (a)   administering to a human or non-human
animal subject a contrast medium comprising a
physiologically compatible complex represented by the
formula:
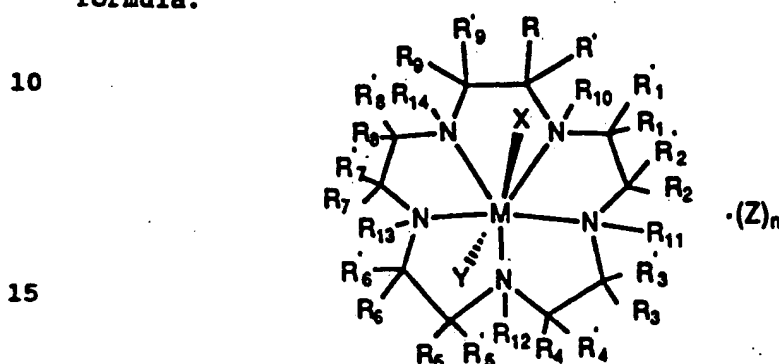
wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5,
R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R', independently are
20 selected from the group consisting of hydrogen, alkyl,
alkenyl, alkynyl, cycloalkyl, cycloalkenyl,
cycloalkylalkyl, cycloalkylcycloalkyl,
cycloalkenylalkyl, alkylcycloalkyl, alkenylcycloalkyl,
alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic,
25 aryl and aralkyl radicals and radicals attached to the
α-carbon of α-amino acids; or R_1 or R'_1 and R_2 or R'_2, R_3
or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7, and
R_8 or R'_8, and R_9 or R', and R or R' together with the
carbon atoms to which they are attached independently
30 form a saturated, partially saturated or unsaturated
cyclic having 3 to 20 carbon atoms; R and R', R_1 and
R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and
R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R', together with
the carbon atoms to which they are attached
35 independently form a saturated, partially saturated, or

unsaturated ring structure having 3 to 20 carbon atoms;
or one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5,
R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and
R_{14} together with a different one of R, R', R_1, R'_1, R_2,
5   R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9,
R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} which is attached to a
different carbon or nitrogen atom in the macrocyclic
ligand may be bound to form a strap represented by the
formula
10   $+ CH_2 +_z M + CH_2 +_w L + CH_2 +_x J + CH_2 +_y$
wherein w, x, y and z independently are integers from 0
to 10, and M, L and J are independently selected from
the group consisting of alkyl, alkenyl, alkynyl, aryl,
cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza,
15 amide, ammonium, thia, sulfonyl, sulfinyl, sulfonamide,
phosphonyl, phosphinyl, phosphino, phosphonium, keto,
ester, carbamate, urea, thiocarbonyl, borates, boranes,
boraza, silyl, siloxy, silaza and combinations thereof;
and R_{10}, R_{11}, R_{12}, R_{13} and R_{14} independently are selected
20 from the group consisting of hydrogen, alkyl, and alkyl
substituted with $-OR_{15}$, $-COOR_{15}$, $-CONR_{15}R_{16}$ or $-PO_3H_2$
wherein R_{15} and R_{16} are independently hydrogen or alkyl;
wherein at least two of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3,
R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are
25 other than hydrogen; wherein X, Y and Z are ligands
independently selected from the group consisting of
halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen,
peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia,
alkylamino, arylamino, heterocycloalkyl amino,
30 heterocycloaryl amino, amine oxides, hydrazine, alkyl
hydrazine, aryl hydrazine, nitric oxide, cyanide,
cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl
nitrile, aryl nitrile, alkyl isonitrile, aryl
isonitrile, nitrate, nitrite, azido, alkyl sulfonic
35 acid, aryl sulfonic acid, alkyl sulfoxide, aryl

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sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid,
aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic
acid, alkyl thiol carboxylic acid, aryl thiol carboxylic
acid, alkyl thiol thiocarboxylic acid, aryl thiol

5   thiocarboxylic acid, alkyl carboxylic acid, aryl
carboxylic acid, urea, alkyl urea, aryl urea, alkyl aryl
urea, thiourea, alkyl thiourea, aryl thiourea, alkyl
aryl thiourea, sulfate, sulfite, bisulfate, bisulfite,
thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine,

10 aryl phosphine, alkyl phosphine oxide, aryl phosphine
oxide, alkyl aryl phosphine oxide, alkyl phosphine
sulfide, aryl phosphine sulfide, alkyl aryl phosphine
sulfide, alkyl phosphonic acid, aryl phosphonic acid,
alkyl phosphinic acid, aryl phosphinic acid, alkyl

15 phosphinous acid, aryl phosphinous acid, phosphate,
thiophosphate, phosphite, pyrophosphite, triphosphate,
hydrogen phosphate, dihydrogen phosphate, alkyl
guanidino, aryl guanidino, alkyl aryl guanidino, alkyl
carbamate, aryl carbamate, alkyl aryl carbamate, alkyl

20 thiocarbamate, aryl thiocarbamate, alkylaryl
thiocarbamate, alkyl dithiocarbamate, aryl
dithiocarbamate, alkylaryl dithiocarbamate, bicarbonate,
carbonate, perchlorate, chlorate, chlorite,
hypochlorite, perbromate, bromate, bromite, hypobromite,

25 tetrahalomanganate, tetrafluoroborate,
hexafluoroantimonate, hypophosphite, iodate, periodate,
metaborate, tetraaryl borate, tetra alkyl borate,
tartrate, salicylate, succinate, citrate, ascorbate,
saccharinate, amino acid, hydroxamic acid, thiotosylate,

30 and anions of ion exchange resins, or the corresponding
anions thereof, or X, Y and Z are independently attached
to one or more of the "R" groups and n is an integer
from 0 to 3;

M is a paramagnetic metal selected from the group

35 consisting of metals having atomic numbers 21-29, 42-44

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and 57-71; and a nontoxic, pharmaceutically acceptable
carrier, adjuvant or vehicle; and

       (b) generating a magnetic resonance image of at
least a part of said subject.
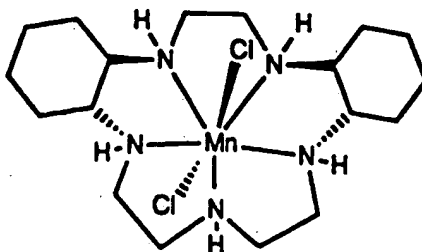
5   2. The method of Claim 1 wherein M is Mn(II) or
Gd(III).

      3. The method of Claim 2 wherein M is Mn(II).

      4. The method of Claim 1 wherein at least three of
R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6,
10 R_7, R'_7, R_8, R'_8, R_9 and R'_9 are other than hydrogen.

      5. The method of Claim 1 wherein at least one of
R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5
and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9 and R
or R' together with the carbon atoms to which they are
15 attached form a saturated cyclic having 5 to 8 carbon
atoms; and all of the remaining "R" groups are
independently selected from hydrogen, alkyl, or alkyl
substituted with $-OR_{15}$ or $-NR_{15}R_{16}$ wherein R_{15} and R_{16} are
independently hydrogen or alkyl.

20   6. The method of Claim 5 wherein said complex is
represented by the formula:

25

      7. The method of Claim 1 wherein at least two of
30 R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6,
R_7, R'_7, R_8, R'_8, R_9 and R'_9 are alkyl or alkyl substituted
with $-OR_{15}$ or $-NR_{15}R_{16}$ wherein R_{15} and R_{16} are independently
hydrogen or alkyl.

      8. The method of Claim 7 wherein said complex is
35 represented by the formula:

5

10
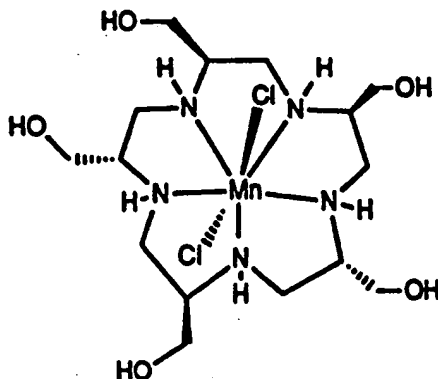
9. A method of diagnostic imaging comprising:

(a) administering to a human or non-human animal
subject a diagnostic agent comprising a physiologically
15 compatible complex represented by the formula:
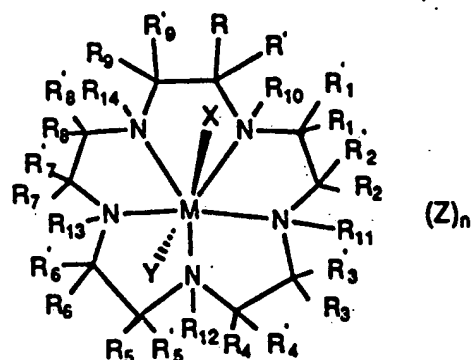
(Z)n

20

25

wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5,
R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently are
selected from the group consisting of hydrogen, alkyl,
alkenyl, alkynyl, cycloalkyl, cycloalkenyl,
30 cycloalkylalkyl, cycloalkylcycloalkyl,
cycloalkenylalkyl, alkylcycloalkyl, alkenylcycloalkyl,
alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic,
aryl and aralkyl radicals and radicals attached to the
α-carbon of α-amino acids; or R_1 or R'_1 and R_2 or R'_2, R_3
35 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and
R_8 or R'_8, and R_9 or R'_9 and R or R' together with the

carbon atoms to which they are attached independently
form a saturated, partially saturated or unsaturated
cyclic having 3 to 20 carbon atoms; R and R', R_1 and R'_1,
R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6,

5   R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9 together with the
carbon atoms to which they are attached independently
form a saturated, partially saturated, or unsaturated
ring structure having 3 to 20 carbon atoms; or one of R,
R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7,

10   R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} together
with a different one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3,
R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11},
R_{12}, R_{13} and R_{14} which is attached to a different carbon or
nitrogen atom in the macrocyclic ligand may be bound to

15   form a strap represented by the formula
$$+ CH_2 +_x\ M + CH_2 +_w\ L + CH_2 +_z\ J + CH_2 +_y$$
wherein w, x, y and z independently are integers from 0
to 10, and M, L and J are independently selected from
the group consisting of alkyl, alkenyl, alkynyl, aryl,
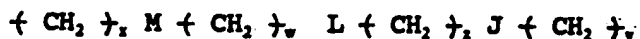
20   cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza,
amide, ammonium, thia, sulfonyl, sulfinyl, sulfonamide,
phosphonyl, phosphinyl, phosphino, phosphonium, keto,
ester, carbamate, urea, thiocarbonyl, borates, boranes,
boraza, silyl, siloxy, silaza and combinations thereof;

25   and R_{10}, R_{11}, R_{12}, R_{13} and R_{14} independently are selected
from the group consisting of hydrogen, alkyl, and alkyl
substituted with $-OR_{15}$, $-COOR_{15}$, $-CONR_{15}R_{16}$ or $-PO_3H_2$
wherein R_{15} and R_{16} are independently hydrogen or alkyl;
wherein at least two of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3,

30   R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are
other than hydrogen; wherein X, Y and Z are ligands
independently selected from the group consisting of
halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen,
peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia,

35   alkylamino, arylamino, heterocycloalkyl amino,

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heterocycloaryl amino, amine oxides, hydrazine, alkyl
hydrazine, aryl hydrazine, nitric oxide, cyanide,
cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl
nitrile, aryl nitrile, alkyl isonitrile, aryl
5 isonitrile, nitrate, nitrite, azido, alkyl sulfonic
acid, aryl sulfonic acid, alkyl sulfoxide, aryl
sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid,
aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic
acid, alkyl thiol carboxylic acid, aryl thiol carboxylic
10 acid, alkyl thiol thiocarboxylic acid, aryl thiol
thiocarboxylic acid, alkyl carboxylic acid, aryl
carboxylic acid, urea, alkyl urea, aryl urea, alkyl aryl
urea, thiourea, alkyl thiourea, aryl thiourea, alkyl
aryl thiourea, sulfate, sulfite, bisulfate, bisulfite,
15 thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine,
aryl phosphine, alkyl phosphine oxide, aryl phosphine
oxide, alkyl aryl phosphine oxide, alkyl phosphine
sulfide, aryl phosphine sulfide, alkyl aryl phosphine
sulfide, alkyl phosphonic acid, aryl phosphonic acid,
20 alkyl phosphinic acid, aryl phosphinic acid, alkyl
phosphinous acid, aryl phosphinous acid, phosphate,
thiophosphate, phosphite, pyrophosphite, triphosphate,
hydrogen phosphate, dihydrogen phosphate, alkyl
guanidino, aryl guanidino, alkyl aryl guanidino, alkyl
25 carbamate, aryl carbamate, alkyl aryl carbamate, alkyl
thiocarbamate, aryl thiocarbamate, alkylaryl
thiocarbamate, alkyl dithiocarbamate, aryl
dithiocarbamate, alkylaryl dithiocarbamate, bicarbonate,
carbonate, perchlorate, chlorate, chlorite,
30 hypochlorite, perbromate, bromate, bromite, hypobromite,
tetrahalomanganate, tetrafluoroborate,
hexafluoroantimonate, hypophosphite, iodate, periodate,
metaborate, tetraaryl borate, tetra alkyl borate,
tartrate, salicylate, succinate, citrate, ascorbate,
35 saccharinate, amino acid, hydroxamic acid, thiotosylate,
and anions of ion exchange resins, or the corresponding

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anions thereof, or X, Y and Z are independently attached
to one or more of the "R" groups and n is an integer
from 0 to 3;
M is a heavy metal selected from the group consisting of
5 metals having atomic numbers 20-32, 42-44, 49 and 57-83;
and a nontoxic, pharmaceutically acceptable carrier,
adjuvant or vehicle; and
        (b) generating an X-ray, ultrasound or
scintigraphic image of at least a part of said subject.
10   10.   The method of Claim 9 wherein M is a
radioactive metal isotope selected from the group
consisting of ^{99m}Tc and ^{111}In and said image is a
scintigraphic image.
        11.   The method of Claim 9 wherein at least three
15 of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6,
R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are other than hydrogen.

        12.   A method of radiotherapy practiced on a human
or non-human animal subject comprising administering to
20 said subject a radioactive agent comprising a
physiologically compatible complex represented by the
formula:

25

30
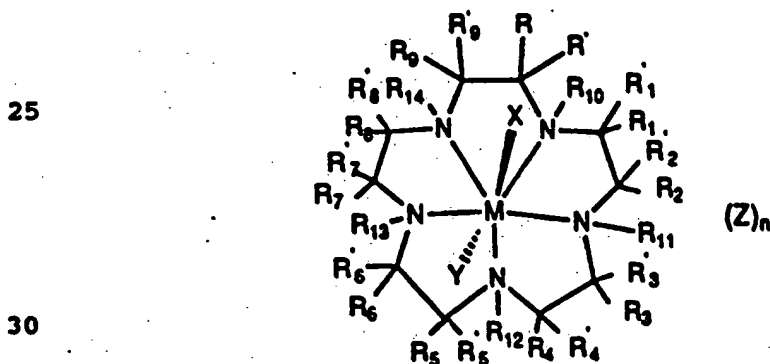
wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5,
R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently are
selected from the group consisting of hydrogen, alkyl,
35 alkenyl, alkynyl, cycloalkyl, cycloalkenyl,
cycloalkylalkyl, cycloalkylcycloalkyl,

cycloalkenylalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals and radicals attached to the α-carbon of α-amino acids; or R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9 and R or R' together with the carbon atoms to which they are attached independently form a saturated, partially saturated or unsaturated cyclic having 3 to 20 carbon atoms; R and R', R_1 and R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9 together with the carbon atoms to which they are attached independently form a saturated, partially saturated, or unsaturated ring structure having 3 to 20 carbon atoms; or one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} together with a different one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} which is attached to a different carbon or nitrogen atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$\text{-(} CH_2 \text{)}_x \text{ M (} CH_2 \text{)}_w \text{ L (} CH_2 \text{)}_z \text{ J (} CH_2 \text{)}_y$$

wherein w, x, y and z independently are integers from 0 to 10, and M, L and J are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, thia, sulfonyl, sulfinyl, sulfonamide, phosphonyl, phosphinyl, phosphino, phosphonium, keto, ester, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and R_{10}, R_{11}, R_{12}, R_{13} and R_{14} independently are selected from the group consisting of hydrogen, alkyl, and alkyl substituted with $-OR_{15}$, $-COOR_{15}$, $-CONR_{15}R_{16}$ or $-PO_3H_2$ wherein R_{15} and R_{16} are independently hydrogen or alkyl; wherein at least two of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3,

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R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are
other than hydrogen; wherein X, Y and Z are ligands
independently selected from the group consisting of
halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen,

5   peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia,
alkylamino, arylamino, heterocycloalkyl amino,
heterocycloaryl amino, amine oxides, hydrazine, alkyl
hydrazine, aryl hydrazine, nitric oxide, cyanide,
cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl

10   nitrile, aryl nitrile, alkyl isonitrile, aryl
isonitrile, nitrate, nitrite, azido, alkyl sulfonic
acid, aryl sulfonic acid, alkyl sulfoxide, aryl
sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid,
aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic

15   acid, alkyl thiol carboxylic acid, aryl thiol carboxylic
acid, alkyl thiol thiocarboxylic acid, aryl thiol
thiocarboxylic acid, alkyl carboxylic acid, aryl
carboxylic acid, urea, alkyl urea, aryl urea, alkyl aryl
urea, thiourea, alkyl thiourea, aryl thiourea, alkyl

20   aryl thiourea, sulfate, sulfite, bisulfate, bisulfite,
thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine,
aryl phosphine, alkyl phosphine oxide, aryl phosphine
oxide, alkyl aryl phosphine oxide, alkyl phosphine
sulfide, aryl phosphine sulfide, alkyl aryl phosphine

25   sulfide, alkyl phosphonic acid, aryl phosphonic acid,
alkyl phosphinic acid, aryl phosphinic acid, alkyl
phosphinous acid, aryl phosphinous acid, phosphate,
thiophosphate, phosphite, pyrophosphite, triphosphate,
hydrogen phosphate, dihydrogen phosphate, alkyl

30   guanidino, aryl guanidino, alkyl aryl guanidino, alkyl
carbamate, aryl carbamate, alkyl aryl carbamate, alkyl
thiocarbamate, aryl thiocarbamate, alkylaryl
thiocarbamate, alkyl dithiocarbamate, aryl
dithiocarbamate, alkylaryl dithiocarbamate, bicarbonate,

35   carbonate, perchlorate, chlorate, chlorite,
hypochlorite, perbromate, bromate, bromite, hypobromite,

tetrahalomanganate, tetrafluoroborate,
hexafluoroantimonate, hypophosphite, iodate, periodate,
metaborate, tetraaryl borate, tetra alkyl borate,
tartrate, salicylate, succinate, citrate, ascorbate,
5 saccharinate, amino acid, hydroxamic acid, thiotosylate,
and anions of ion exchange resins, or the corresponding
anions thereof, or X, Y and Z are independently attached
to one or more of the "R" groups and n is an integer
from 0 to 3;

10 M is a radioactive metal selected from ^{153}Sm, ^{67}Cu or ^{90}Y;
and a nontoxic, pharmaceutically acceptable carrier,
adjuvant or vehicle.

13. A compound represented by the formula:

15

20
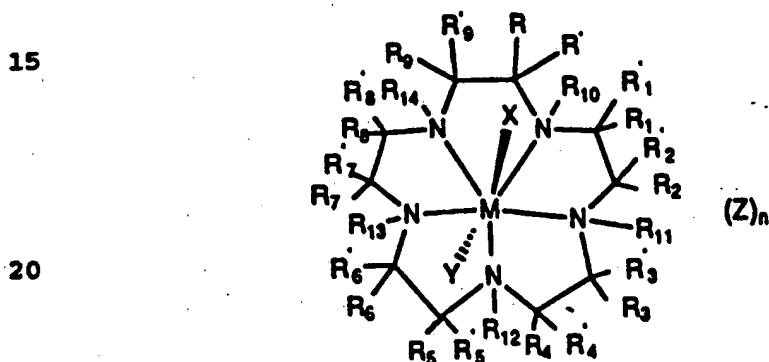
wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5,
R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently are
25 selected from the group consisting of hydrogen, alkyl,
alkenyl, alkynyl, cycloalkyl, cycloalkenyl,
cycloalkylalkyl, cycloalkylcycloalkyl,
cycloalkenylalkyl, alkylcycloalkyl, alkenylcycloalkyl,
alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic,
30 aryl and aralkyl radicals and radicals attached to the
α-carbon of α-amino acids; or R_1 or R'_1 and R_2 or R'_2, R_3
or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and
R_8 or R'_8, and R_9 or R'_9 and R or R' together with the
carbon atoms to which they are attached independently
35 form a saturated, partially saturated or unsaturated

cyclic having 3 to 20 carbon atoms; R and R', R_1 and
R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and
R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9 together with
the carbon atoms to which they are attached
5   independently form a saturated, partially saturated, or
unsaturated ring structure having 3 to 20 carbon atoms;
or one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5,
R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and
R_{14} together with a different one of R, R', R_1, R'_1, R_2,
10 R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9,
R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} which is attached to a
different carbon or nitrogen atom in the macrocyclic
ligand may be bound to form a strap represented by the
formula
15      $\text{-}(CH_2)_w\ M\ (CH_2)_x\ \ L\ (CH_2)_y\ J\ (CH_2)_z\text{-}$
wherein w, x, y and z independently are integers from 0
to 10, and M, L and J are independently selected from
the group consisting of alkyl, alkenyl, alkynyl, aryl,
cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza,
20 amide, ammonium, thia, sulfonyl, sulfinyl, sulfonamide,
phosphonyl, phosphinyl, phosphino, phosphonium, keto,
ester, carbamate, urea, thiocarbonyl, borates, boranes,
boraza, silyl, siloxy, silaza and combinations thereof;
and R_{10}, R_{11}, R_{12}, R_{13} and R_{14} independently are selected
25 from the group consisting of hydrogen, alkyl, and alkyl
substituted with $-OR_{15}$, $-COOR_{15}$, $-CONR_{15}R_{16}$ or $-PO_3H_2$
wherein R_{15} and R_{16} are independently hydrogen or alkyl;
wherein at least two of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3,
R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are
30 other than hydrogen;
wherein X, Y and Z are ligands independently selected
from the group consisting of halide, oxo, aquo, hydroxo,
alcohol, phenol, dioxygen, peroxo, hydroperoxo,
alkylperoxo, arylperoxo, ammonia, alkylamino, arylamino,
35 heterocycloalkyl amino, heterocycloaryl amino, amine

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oxides, hydrazine, alkyl hydrazine, aryl hydrazine,
nitric oxide, cyanide, cyanate, thiocyanate, isocyanate,
isothiocyanate, alkyl nitrile, aryl nitrile, alkyl
isonitrile, aryl isonitrile, nitrate, nitrite, azido,
5 alkyl sulfonic acid, aryl sulfonic acid, alkyl
sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl
sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid,
aryl sulfinic acid, alkyl thiol carboxylic acid, aryl
thiol carboxylic acid, alkyl thiol thiocarboxylic acid,
10 aryl thiol thiocarboxylic acid, alkyl carboxylic acid,
aryl carboxylic acid, urea, alkyl urea, aryl urea, alkyl
aryl urea, thiourea, alkyl thiourea, aryl thiourea,
alkyl aryl thiourea, sulfate, sulfite, bisulfate,
bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl
15 phosphine, aryl phosphine, alkyl phosphine oxide, aryl
phosphine oxide, alkyl aryl phosphine oxide, alkyl
phosphine sulfide, aryl phosphine sulfide, alkyl aryl
phosphine sulfide, alkyl phosphonic acid, aryl
phosphonic acid, alkyl phosphinic acid, aryl phosphinic
20 acid, alkyl phosphinous acid, aryl phosphinous acid,
phosphate, thiophosphate, phosphite, pyrophosphite,
triphosphate, hydrogen phosphate, dihydrogen phosphate,
alkyl guanidino, aryl guanidino, alkyl aryl guanidino,
alkyl carbamate, aryl carbamate, alkyl aryl carbamate,
25 alkyl thiocarbamate, aryl thiocarbamate, alkylaryl
thiocarbamate, alkyl dithiocarbamate, aryl
dithiocarbamate, alkylaryl dithiocarbamate, bicarbonate,
carbonate, perchlorate, chlorate, chlorite,
hypochlorite, perbromate, bromate, bromite, hypobromite,
30 tetrahalomanganate, tetrafluoroborate,
hexafluoroantimonate, hypophosphite, iodate, periodate,
metaborate, tetraaryl borate, tetra alkyl borate,
tartrate, salicylate, succinate, citrate, ascorbate,
saccharinate, amino acid, hydroxamic acid, thiotosylate,
35 and anions of ion exchange resins, or the corresponding
anions thereof, or X, Y and Z are independently attached

to one or more of the "R" groups and n is an integer
from 0 to 3;

M is a paramagnetic metal selected from the group
consisting of metals having atomic numbers 21-29, 42-44

5   and 57-71; and

at least one of R_{10}, R_{11}, R_{12}, R_{13} and R_{14} is other than
hydrogen.

14.   The compound of Claim 13 wherein M is Mn(II)
or Gd(III).

10   15.   The compound of Claim 13 wherein at least
three of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5,
R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are other than
hydrogen.

16.   The compound of Claim 13 wherein at least one

15   of R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or
R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9
and R or R' together with the carbon atoms to which they
are attached form a saturated cyclic having 5 to 8
carbon atoms; and all of the remaining "R" groups are

20   independently selected from hydrogen, alkyl, or alkyl
substituted with $-OR_{15}$ or $-NR_{15}R_{16}$ wherein R_{15} and R_{16} are
independently hydrogen or alkyl.

17.   The compound of Claim 13 wherein at least two
of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6,

25   R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are alkyl or alkyl
substituted with $-OR_{15}$ or $-NR_{15}R_{16}$ wherein R_{15} and R_{16} are
independently hydrogen or alkyl.

INTERNATIONAL SEARCH REPORT

Inter.   nal Application No
PCT/US 95/03763

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6   A61K49/00   A61K51/04   C07F13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6   A61K   C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category°	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 296 522 (DOW CHEMICAL CO) 28 December 1988 see claims	9-12
X	EP,A,0 287 465 (GUERBET SA) 19 October 1988 see page 8, line 56 - page 9, line 21; claims	1-5,7, 13-17
X	DE,A,24 61 919 (DU PONT) 17 July 1975 see page 6; figure X; table I see page 1, paragraph 1	13
X	WO,A,92 04919 (MALLINCKRODT MEDICAL INC) 2 April 1992 see claims	1-5, 13-17

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[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 July 1995

Date of mailing of the international search report

01.08.95

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Authorized officer

BERTE, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 21017 (UNGER EVAN C ;SHEN DEKANG (US)) 26 November 1992 see page 5; figure III see claims 42,50,77,86 ---	1-5, 13-17
P,X	TETRAHEDRON LETT. (1994), 35(22), 3687-90 CODEN: TELEAY;ISSN: 0040-4039, ASTON, KARL W. ET AL 'Asymmetric synthesis of highly functionalized polyazamacrocycles via reduction of cyclic peptide precursors' see the whole document ---	13-17
X,P	TETRAHEDRON LETT. (1994), 35(6), 853-6 CODEN: TELEAY;ISSN: 0040-4039, 4 LENNON, PATRICK J. ET AL 'New conformationally constrained polyazamacrocycles prepared via the bis(chloroacetamide) method' see page 853, paragraph 1; figures 17,18 ---	5-7, 13-17
X	EP,A,0 524 161 (MONSANTO CO) 20 January 1993 see page 2, line 54 - page 4, line 15; claims ---	13-17
A	WO,A,82 04252 (BORREGAARD IND ;DALE JOHANNES (NO); BUOEN SOLFRID (NO); KRANE JOST) 9 December 1982 ---	1-17
X	FR,A,2 246 555 (DU PONT) 2 May 1975 see claims 1,9,10 ---	13-17
P,A	WO,A,94 15925 (MONSANTO CO) 21 July 1994 see claims ---	1-17
X	CHEMICAL ABSTRACTS, vol. 110, no. 16, 17 April 1989, Columbus, Ohio, US; abstract no. 146606, NEWTON, JAMES E. ET AL 'Synthesis and characterization of the manganese(II) complex of [15]aneN5' see abstract & J. COORD. CHEM. (1988), 19(1-3), 265-77 CODEN: JCCMBQ;ISSN: 0095-8972, ---	13,14
A	PATENT ABSTRACTS OF JAPAN vol. 15, no. 461 (C-0887) 22 November 1991 & JP,A,03 197 468 (TEIJIN LTD) 28 August 1991 see abstract ---	1-17

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 12, no. 219 (C-506) 22 June 1988 & JP,A,63 014 780 (TOSOH CORP.) 21 January 1988 see abstract -----	1-17

Inte...ational application No.

PCT/US95/03763

Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:
   Remark:Although claims 1-12 are directed to a method of treatment of (dia-
   gnostic method practised on) the human/animal body the search has been car-
   ried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-5,7,9-17
   because they relate to parts of the international application that do not comply with the prescribed requirements to such
   an extent that no meaningful international search can be carried out, specifically:
   please see enclosure ../..!

3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all
   searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment
   of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report
   covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is
   restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest   [ ] The additional search fees were accompanied by the applicant's protest.

                                         [ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM   PCT/ISA/210

Incomplete search,...
II. Obscurities, ...
In view of the definition of products by means of their biological, chemical
and/or pharmacological properties, the search has to be restricted for eco-
nomic reasons.
The search was limited to the compounds for which pharmacological data was
given and/or the compounds mentioned in the claims or examples.
(See Guidelines, Part B, Chapt. III, paragraph 3.6)

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